

Dosage form that is secured against misuse

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Cited documents:

 EP1166776 (A2)
 EP1138321 (A2)
 WO0152651 (A2)
 US2003068392 (A1)

Abstract of EP 1859789 (A1)

Abuse-proofed, thermoformed dosage form (C1) comprises an active ingredient with abuse potential (A) optionally together with physiologically acceptable auxiliary substances (B), synthetic or natural polymer (P1) and optionally at least one wax (D). (P1) Exhibits a breaking strength of at least 500 N. An independent claim is included for: preparation of (C1) which comprises mixing components (A), (B), (P1) and the other optional components, followed by pressing the resultant mixture, optionally after granulation (preferably by a melt process), to yield (C1) with preceding, simultaneous, or subsequent exposure to heat.
 - ACTIVITY : None given - MECHANISM OF ACTION : None given.

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Bemerkungen:

Diese Anmeldung ist am 29 - 11 - 2006 als  
Teilanmeldung zu der unter INID-Kode 62 erwähnten  
Anmeldung eingereicht worden.

(54) **Gegen Missbrauch gesicherte Darreichungsform**

(57) Die vorliegende Erfindung betrifft eine gegen  
Missbrauch gesicherte, ohne Extrusion thermogeformte  
Darreichungsform enthaltend neben einem oder mehreren  
Wirkstoffen mit Mißbrauchspotential sowie ggf. physiologisch  
verträglichen Hilfsstoffen mindestens ein syn-

thetisches oder natürliches Polymer mit einer Bruchfestigkeit  
von mindestens 500 N und deren Verfahren zur Herstellung.

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**Beschreibung**

**[0001]** Die vorliegende Erfindung betrifft eine gegen Missbrauch gesicherte, ohne Extrusion thermogeformte Darreichungsform enthaltend neben einem oder mehreren Wirkstoffen mit Missbrauchspotential (A) sowie ggf. physiologisch verträglichen Hilfsstoffen (B) mindestens ein synthetisches oder natürliches Polymer (C) und ggf. mindestens ein Wachs (D), wobei die Komponente (C) sowie die gegebenenfalls vorhandene Komponente (D) jeweils eine Bruchfestigkeit von mindestens 500 N aufweist, sowie ein Verfahren zur Herstellung der erfindungsgemäßen Darreichungsform.

**[0002]** Eine Vielzahl von pharmazeutischen Wirkstoffen weist neben einer ausgezeichneten Wirksamkeit auf ihrem betreffenden Anwendungsgebiet auch ein Mißbrauchspotential auf, d.h. sie können von einem Mißbraucher eingesetzt werden, um Wirkungen herbeizuführen, die nicht ihrem Bestimmungszweck entsprechen. So werden beispielsweise Opiate, die eine exzellente Wirksamkeit bei der Bekämpfung von starken bis sehr starken Schmerzen zeigen, von Mißbrauchern häufig zum Einleiten rauschartiger, euphorisierender Zustände verwendet.

**[0003]** Um Missbrauch zu ermöglichen, werden die entsprechenden Darreichungsformen wie Tabletten oder Kapseln vom Mißbraucher zerkleinert, z. B. gemörsert, der Wirkstoff aus dem so erhaltenen Pulver mit Hilfe einer vorzugsweise wässrigen Flüssigkeit extrahiert und die resultierende Lösung, ggf. nach Filtration durch Watte oder Zellstoff, parenteral, insbesondere intravenös, appliziert. Bei dieser Art der Verabreichung kommt es zu einem gegenüber der oralen, missbräuchlichen Applikation noch zusätzlich beschleunigten Anfluten des Wirkstoffes mit dem vom Mißbraucher gewünschten Ergebnis, nämlich dem Kick. Dieser Kick wird auch erreicht, wenn die gepulverte Darreichungsform nasal appliziert, d. h. geschnupft wird. Da retardierte, orale Darreichungsformen, die Wirkstoffe mit Mißbrauchspotential enthalten, üblicherweise selbst bei einer oralen Einnahme von missbräuchlich hohen Mengen nicht zu dem vom Mißbraucher gewünschten Kick führen, werden auch diese zum Missbrauch zerkleinert und extrahiert.

**[0004]** Zur Verhinderung des Missbrauchs wurde in dem US-A- 4,070,494 vorgeschlagen, der Darreichungsform ein quellbares Mittel zuzusetzen. Dieses quillt bei der Zugabe von Wasser zur Extraktion des Wirkstoffes auf und bewirkt, dass das vom Gel separierte Filtrat nur eine geringe Menge an Wirkstoff enthält.

**[0005]** Ein entsprechender Ansatz zur Verhinderung des parenteralen Mißbrauchs liegt auch der in der WO 95/20947 offenbarten Mehrschichttablette zugrunde, die den Wirkstoff mit Mißbrauchspotential und mindestens einen Gelbildner jeweils in unterschiedlichen Schichten getrennt aufweist.

**[0006]** Ein weiterer Ansatz zur Verhinderung des parenteralen Mißbrauchs wird in der WO 03/015531 A2 offenbart. Dort wird eine Darreichungsform enthaltend ein analgetisches Opioid und einen Farbstoff als aversives Mittel beschrieben. Die Farbe, die durch unzulässige Manipulation der Darreichungsform freigesetzt wird, soll den Mißbraucher davon abhalten, diese manipulierte Darreichungsform zu verwenden.

**[0007]** Eine weitere bekannte Möglichkeit zur Erschwerung des Missbrauchs besteht darin, der Darreichungsform Antagonisten der Wirkstoffe, wie z. B. Naloxon oder Naltexon im Fall von Opioiden, oder Verbindungen, die zu physiologischen Abwehrreaktionen führen, wie z. B. Raolix ipecacuama = Brechwurz, der Darreichungsform zuzusetzen.

**[0008]** Da aber nach wie vor in den meisten Fällen für den Missbrauch, eine Pulverisierung der Darreichungsformen mit einem zum Missbrauch geeigneten Wirkstoff notwendig ist, war es Aufgabe der vorliegenden Erfindung, die dem Missbrauch vorangehende Pulverisierung der Darreichungsform mit den einem potentiellen Mißbraucher üblicherweise zur Verfügung stehenden Mitteln zu erschweren bzw. zu verhindern und somit eine feste Darreichungsform für Wirkstoffe mit Missbrauchspotential zur Verfügung zu stellen, die bei bestimmungsgemäßer Applikation die gewünschte therapeutische Wirkung gewährleistet, aus der aber die Wirkstoffe nicht durch einfaches Pulverisieren in eine zum Missbrauch geeignete Form übergeführt werden können.

**[0009]** Diese Aufgabe wurde durch die Bereitstellung der erfindungsgemäßen, gegen Missbrauch gesicherten, ohne Extrusion thermogeformten Darreichungsform, die neben einem oder mehreren Wirkstoffen mit Mißbrauchspotential (A) mindestens ein synthetisches oder natürliches Polymer (C) und ggf. mindestens ein Wachs (D) enthält, wobei die Komponente (C) und die gegebenenfalls vorhandene Komponente (D) jeweils eine Bruchfestigkeit von mindestens 500 N aufweist, gelöst.

**[0010]** Durch den Einsatz von Polymeren mit der angegebenen Mindestbruchfestigkeit (gemessen, wie in der Anmeldung angegeben), vorzugsweise in solchen Mengen, dass auch die Darreichungsform eine solche Mindestbruchfestigkeit von mindestens 500 N aufweist, gelingt es, ein Pulverisieren der Darreichungsform mit üblichen Mitteln zu verhindern und damit den anschließenden Missbrauch erheblich zu erschweren bzw. zu unterbinden.

**[0011]** Ohne ausreichende Zerkleinerung ist nämlich eine parenteral, insbesondere intravenöse, gefahrlose Applikation nicht möglich oder die Extraktion des Wirkstoffes daraus dauert für den Mißbraucher zu lange bzw. ein Kick bei missbräuchlicher, oralen Einnahme erfolgt nicht, da keine spontane Freisetzung passiert.

**[0012]** Unter einer Zerkleinerung wird erfindungsgemäß die Pulverisierung der Darreichungsform mit üblichen Mitteln, die einem Mißbraucher üblicherweise zur Verfügung stehen, wie z. B. ein Mörser und Pistill, ein Hammer, ein Schlegel oder andere gebräuchliche Mittel zum Pulverisieren unter Krafteinwirkung verstanden.

**[0013]** Die erfindungsgemäße Darreichungsform ist daher zur Verhinderung des parenteralen, nasalen und/oder oralen Missbrauchs von Wirkstoffen, vorzugsweise von pharmazeutischen Wirkstoffen, mit Mißbrauchspotential geeignet.

[0014] Pharmazeutische Wirkstoffe mit Mißbrauchspotential sind dem Fachmann ebenso wie deren einzusetzende Mengen und Verfahren zu deren Herstellung bekannt und können als solche, in Form ihrer dementsprechenden Derivate, insbesondere Ester oder Ether, oder jeweils in Form entsprechender physiologisch verträglicher Verbindungen, insbesondere in Form ihrer entsprechenden Salze oder Solvate, als Racemate oder Stereoisomere in der erfindungsgemäßen Darreichungsform vorliegen. Die erfindungsgemäße Darreichungsform eignet sich auch für die Verabreichung von mehreren pharmazeutischen Wirkstoffen in einer Darreichungsform. Vorzugsweise erhält die Darreichungsform nur einen bestimmten Wirkstoff.

[0015] Die erfindungsgemäße Darreichungsform eignet sich insbesondere zur Verhinderung des Missbrauchs wenigstens eines pharmazeutischen Wirkstoffs, der ausgewählt ist aus der Gruppe umfassend Opiode, Tranquillantien, vorzugsweise Benzodiazepine, Barbiturate, Stimulantien und weitere Betäubungsmittel.

[0016] Ganz besonders eignet sich die erfindungsgemäße Darreichungsform zur Verhinderung des Mißbrauchs eines Opioids, Tranquillanz oder eines anderen Betäubungsmittels, das ausgewählt ist aus der Gruppe umfassend N-[1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-methoxymethyl-4-piperidyl]propionanilid (Alfentanil), 5,5-Diallylbarbitursäure (Allobarbit), Allylprodin, Alphaprodin, 8-Chlor-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]-benzodiazepin (Alprazolam), 2-Diethylaminopropiophenon (Amfepramon), ( $\pm$ )- $\alpha$ -Methylphenethylamin (Amfetamin), 2-( $\alpha$ -Methylphenethylamino)-2-phenylacetonitril (Amfetaminil), 5-Ethyl-5-isopentylbarbitursäure (Amobarbital), Anileridin, Apocodein, 5,5-Diethylbarbitursäure (Barbital), Benzylmorphin, Bezitramid, 7-Brom-5-(2-pyridyl)-1H-1,4-benzodiazepin-2(3H)-on (Bromazepam), 2-Brom-4-(2-chlorphenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin (Brotizolam), 17-Cyclopropylmethyl-4,5 $\alpha$ -epoxy-7 $\alpha$ [(S)-1-hydroxy-1,2,2-trimethyl-propyl]-6-methoxy-6,14-endo-ethanomorphinan-3-ol (Buprenorphin), 5-Butyl-5-ethylbarbitursäure (Butobarbital), Butorphanol, (7-Chlor-1,3-dihydro-1-methyl-2-oxo-5-phenyl-2H-1,4-benzodiazepin-3-yl)-dimethyl-carbammat (Camazepam), (1S,2S)-2-Amino-1-phenyl-1-propanol (Cathin / D-Norpseudoephedrin), 7-Chlor-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-ylamin-4-oxid (Chlordiazepoxid), 7-Chlor-1-methyl-5-phenyl-1H-1,5-benzodiazepin-2,4(3H,5H)-dion (Clobazam), 5-(2-Chlorphenyl)-7-nitro-1H-1,4-benzodiazepin-2(3H)-on (Clonazepam), Clonitazen, 7-Chlor-2,3-dihydro-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-carbonsäure (Clorazepat), 5-(2-Chlorphenyl)-7-ethyl-1-methyl-1H-thieno[2,3-e][1,4]diazepin-2(3H)-on (Clotiazepam), 10-Chlor-11b-(2-chlorphenyl)-2,3,7,11b-tetrahydrooxazolo[3,2-d][1,4]benzodiazepin-6(5H)-on (Cloxazolam), (-)-Methyl-3 $\beta$ -benzoyloxy-2 $\beta$ [(1 $\alpha$ H,5 $\alpha$ H)-tropancarboxylat] (Cocain), 4,5 $\alpha$ -Epoxy-3-methoxy-17-methyl-7-morphinen-6 $\alpha$ -ol (Codein), 5-(1-Cyclohexenyl)-5-ethylbarbitursäure (Cyclobarbit), Cyclophan, Cyprenorphin, 7-Chlor-5-(2-chlorphenyl)-1H-1,4-benzodiazepin-2(3H)-on (Delorazepam), Desomorphin, Dextromoramid, (+)-(1-Benzyl-3-dimethylamino-2-methyl-1-phenylpropyl)propionat (Dextropropoxyphen), Dezocin, Diampromid, Diamorphon, 7-Chlor-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2(3H)-on (Diazepam), 4,5 $\alpha$ -Epoxy-3-methoxy-17-methyl-6 $\alpha$ -morphinanol (Dihydrocodein), 4,5 $\alpha$ -Epoxy-17-methyl-3,6 $\alpha$ -morphinandiol (Dihydromorphin), Dimenoxadol, Dimethetamol, Dimethylthiambuten, Dioxaphetylbutyrat, Dipipanone, (6aR,10aR)-6,6,9-Trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol (Dronabinol), Eptazocin, 8-Chlor-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin (Estazolam), Ethoheptazin, Ethylmethylthiambuten, Ethyl-[7-chlor-5-(2-fluorphenyl)-2,3-dihydro-2-oxo-1H-1,4-benzodiazepin-3-carboxylat] (Ethyllofiazepat), 4,5 $\alpha$ -Epoxy-3-ethoxy-17-methyl-7-morphinen-6 $\alpha$ -ol (Ethylmorphin), Etonitazen, 4,5 $\alpha$ -Epoxy-7 $\alpha$ -(1-hydroxy-1-methylbutyl)-6-methoxy-17-methyl-6,14-endo-etheno-morphinan-3-ol (Etorphin), N-Ethyl-3-phenyl-8,9,10-trinorbornan-2-ylamin (Fencamfamin), 7-[2-( $\alpha$ -Methylphenethylamino)ethyl]-theophyllin (Fenetyllin), 3-( $\alpha$ -Methylphenethylamino)propionitril (Fenproporex), N-(1-Phenethyl-4-piperidyl)propionanilid (Fentanyl), 7-Chlor-5-(2-fluorphenyl)-1-methyl-1H-1,4-benzodiazepin-2(3H)-on (Fludiazepam), 5-(2-Fluorphenyl)-1-methyl-7-nitro-1H-1,4-benzodiazepin-2(3H)-on (Flunitrazepam), 7-Chlor-1-(2-diethylaminoethyl)-5-(2-fluorphenyl)-1H-1,4-benzodiazepin-2(3H)-on (Flurazepam), 7-Chlor-5-phenyl-1-(2,2,2-trifluorethyl)-1H-1,4-benzodiazepin-2(3H)-on (Halazepam), 10-Brom-11b-(2-fluorphenyl)-2,3,7,11b-tetrahydro[1,3]oxazolo[3,2-d][1,4]benzodiazepin-6(5H)-on (Haloxazolam), Heroin, 4,5 $\alpha$ -Epoxy-3-methoxy-17-methyl-6-morphinanon (Hydrocodon), 4,5 $\alpha$ -Epoxy-3-hydroxy-17-methyl-6-morphinanon (Hydromorphon), Hydroxypethidin, Isomethadon, Hydroxymethylmorphinan, 11-Chlor-8,12b-dihydro-2,8-dimethyl-12b-phenyl-4H-[1,3]oxazino[3,2-d][1,4]benzodiazepin-4,7(6H)-dion (Ketazolam), 1-[4-(3-Hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanon (Ketobemidon), (3S,6S)-6-Dimethylamino-4,4-diphenylheptan-3-ylacetat (Levacetylmethadol (LAAM)), (-)-6-Dimethylamino-4,4-diphenyl-3-heptanon (Levomethadon), (-)-17-Methyl-3-morphinanol (Levorphanol), Levophenacetylmorphan, Lofentanil, 6-(2-Chlorphenyl)-2-(4-methyl-1-piperazinylmethyl)-8-nitro-2H-imidazo[1,2-a][1,4]benzodiazepin-1(4H)-on (Loprazolam), 7-Chlor-5-(2-chlorphenyl)-3-hydroxy-1H-1,4-benzodiazepin-2(3H)-on (Lorazepam), 7-Chlor-5-(2-chlorphenyl)-3-hydroxy-1-methyl-1H-1,4-benzodiazepin-2(3H)-on (Lormetazepam), 5-(4-Chlorphenyl)-2,5-dihydro-3H-imidazo[2,1-a]isoindol-5-ol (Mazindol), 7-Chlor-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin (Medazepam), N-(3-Chlorpropyl)- $\alpha$ -methylphenethylamin (Mefenorex), Meperidin, 2-Methyl-2-propyltrimethylendicarbamat (Meprobamat), Meptazinol, Metazocin, Methylmorphin, N, $\alpha$ -Dimethylphenethylamin (Metamfetamin), ( $\pm$ )-6-Dimethylamino-4,4-diphenyl-3-heptanon (Methadon), 2-Methyl-3- $\alpha$ -tolyl-4(3H)-chinazolinon (Methaqualon), Methyl-[2-phenyl-2-(2-piperidyl)acetat] (Methylphenidat), 5-Ethyl-1-methyl-5-phenylbarbitursäure (Methylphenobarbital), 3,3-Diethyl-5-methyl-2,4-piperidindion (Methyprylon), Metopon, 8-Chlor-6-(2-fluorphenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepin (Midazolam), 2-(Benzhydrylsulfinyl)acetamid (Modafinil), 4,5 $\alpha$ -Epoxy-17-methyl-7-morphinen-3,6 $\alpha$ -diol (Morphin), Myrophin, ( $\pm$ )-trans-3-(1,1-Dimethylheptyl)-

7,8,10,10 $\alpha$ -tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo [*b*, *d*]pyran-9(6*αH*)-on (Nabilon), Nalbuphen, Nalorphin, Narcein, Nicomorphin, 1-Methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-on (Nimetazepam), 7-Nitro-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-on (Nitrazepam), 7-Chlor-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-on (Nordazepam), Norlevorphanol, 6-Dimethylamino-4,4-diphenyl-3-hexanon (Normethadon), Normorphin, Norpipanone, der geronnene Saft der zur Art *Papaver somniferum* gehörenden Pflanzen (Opium), 7-Chlor-3-hydroxy-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-on (Oxazepam), (*cis-trans*)-10-Chlor-2,3,7,11b-tetrahydro-2-methyl-11b-phenyloxazolo[3,2-*d*][1,4] benzodiazepin-6-(5*H*)-on (Oxazolam), 4,5 $\alpha$ -Epoxy-14-hydroxy-3-methoxy-17-methyl-6-morphinanon (Oxycodon), Oxymorphon, Pflanzen und Pflanzenteile der zur Art *Papaver somniferum* (einschließlich der Unterart *setigerum*) gehörenden Pflanzen (*Papaver somniferum*), *Papaveretum*, 2-Imino-5-phenyl-4-oxazolidinon (Pemolin), 1,2,3,4,5,6-Hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (Pentazocin), 5-Ethyl-5-(1-methylbutyl)-barbitursäure (Pentobarbital), Ethyl-(1-methyl-4-phenyl-4-piperidincarboxylat) (Pethidin), Phenadoxon, Phenomorphan, Phenazocin, Phenoperidin, Piminodin, Pholcodein, 3-Methyl-2-phenylmorpholin (Phenmetrazin), 5-Ethyl-5-phenylbarbitursäure (Phenobarbital),  $\alpha,\alpha$ -Dimethylphenethylamin (Phentermin), 7-Chlor-5-phenyl-1-(2-propinyl)-1*H*-1,4-benzodiazepin-2(3*H*)-on (Pinazepam),  $\alpha$ -(2-Piperidyl)benzhydrolalkohol (Pipradrol), 1'-(3-Cyan-3,3-diphenylpropyl)[1,4'-bipiperidin]-4'-carboxamid (Piritramid), 7-Chlor-1-(cyclopropylmethyl)-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-on (Prazepam), Profadol, Proheptazin, Promedol, Properidin, Propoxyphen, N-(1-Methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamid, Methyl {3-[4-methoxycarbonyl-4-(*N*-phenylpropanamido)piperidino]propanoat} (Remifentanyl), 5-sec-Butyl-5-ethylbarbitursäure (Secbutabarbital), 5-Allyl-5-(1-methylbutyl)-barbitursäure (Secobarbital), *N*-[4-Methoxymethyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilid (Sufentanyl), 7-Chlor-2-hydroxy-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2(3*H*)-on (Temazepam), 7-Chlor-5-(1-cyclohexenyl)-1-methyl-1*H*-1,4-benzodiazepin-2(3*H*)-on (Tetrazepam), Ethyl-(2-dimethylamino-1-phenyl-3-cyclohexen-1-carboxylat) (Tilidin (*cis* und *trans*)), Tramadol, 8-Chlor-6-(2-chlorphenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin (Triazolam), 5-(1-Methylbutyl)-5-vinylbarbitursäure (Vinylbital), (1*R*,2*R*)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (1*R*, 2*R*, 4*S*)-2-[Dimethylamino)methyl-4-(*p*-fluorbenzyloxy)-1-(*m*-methoxyphenyl)cyclohexanol, (1*R*, 2*R*)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, (1*S*, 2*S*)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (2*R*, 3*R*)-1-Dimethylamino-3-(3-Methoxy-phenyl)-2-methyl-pentan-3-ol, (1*RS*, 3*RS*, 6*RS*)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, vorzugsweise als Racemat, 3-(2-Dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-(4-isobutyl-phenyl)-propionat, 3-(2-Dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-xpropionat, 3-(2-Dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)-propionat, 3-(2-Dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)-propionat, (RR-SS)-2-Acetoxy-4-trifluoromethyl-benzoesäure 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-Hydroxy-4-trifluoromethyl-benzoesäure 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-Chloro-2-hydroxy-benzoesäure 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-Hydroxy-4-methyl-benzoesäure 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-Hydroxy-4-methoxy-benzoesäure 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl-ester, (RR-SS)-2-Hydroxy-5-nitro-benzoesäure 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-Difluoro-3-hydroxy-biphenyl-4-carbonsäure 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester sowie entsprechende stereoisomere Verbindungen, jeweils deren entsprechende Derivate, insbesondere Amide, Ester oder Ether, und jeweils deren physiologisch verträgliche Verbindungen, insbesondere deren Salze und Solvate, besonders bevorzugt Hydrochloride.

**[0017]** Die erfindungsgemäße Darreichungsform eignet sich insbesondere zur Verhinderung des Missbrauchs eines opioiden Wirkstoffes ausgewählt aus der Gruppe umfassend Oxycodon, Hydromorphon, Morphin, Tramadol und deren physiologisch verträgliche Derivate oder Verbindungen, vorzugsweise deren Salze und Solvate, vorzugsweise deren Hydrochloride.

**[0018]** Weiterhin eignet sich die erfindungsgemäße Darreichungsform insbesondere zur Verhinderung des Missbrauchs eines opioiden Wirkstoffes ausgewählt aus der Gruppe umfassend (1*R*, 2*R*)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol, (2*R*, 3*R*)-1-Dimethylamino-3-(3-methoxy-phenyl)-2-methyl-pentan-3-ol, (1*RS*, 3*RS*, 6*RS*)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexan-1,3-diol, (1*R*, 2*R*)-3-(2-Dimethylaminomethyl-cyclohexyl)-phenol, deren physiologisch verträglichen Salze, vorzugsweise Hydrochloride, physiologisch verträgliche Enantiomere, Stereoisomere, Diastereomere und Racemate und deren physiologisch verträglichen Derivate, vorzugsweise Ether, Ester oder Amide.

**[0019]** Diese Verbindungen bzw. deren Herstellungsverfahren sind in der EP-A-693475 bzw. EP-A-780369 beschrieben. Die entsprechenden Beschreibungen werden hiermit als Referenz eingeführt und gelten als Teil der Offenbarung.

**[0020]** Zur Erzielung der notwendigen Bruchfestigkeit der erfindungsgemäßen Darreichungsform werden mindestens ein synthetisches oder natürliches Polymer (C) mit einer Bruchfestigkeit, gemessen nach der in der vorliegenden Anmeldung offenbarten Methode, von mindestens 500 N eingesetzt. Bevorzugt wird hierfür mindestens ein Polymeres ausgewählt aus der Gruppe umfassend Polyalkylenoxide, vorzugsweise Polymethylenoxid, Polyethylenoxid, Polypropylenoxid; Polyethylen, Polypropylen, Polyvinylchlorid, Polycarbonat, Polystyrol, Polyacrylat, deren Copolymerisate und Mischungen aus mindestens zwei der genannten Polymeren eingesetzt. Bevorzugt sind hochmolekulare, thermoplastische Polyalkylenoxide. Besonders bevorzugt sind hochmolekulare Polyethylenoxide mit einem Molekulargewicht von

mindestens 0,5 Mio., vorzugsweise mindestens 1 Mio. bis 15 Mio., bestimmt durch rheologische Messungen. Diese Polymeren weisen eine Viskosität bei 25 °C von 4500 bis 17600 cP, gemessen an einer 5 Gew.% wässrigen Lösung mit Hilfe eines Brookfield Viskosimeter, Model RVF (Spindel Nr. 2 / Rotationsgeschwindigkeit 2 rpm), von 400 bis 4000 cP, gemessen an einer 2 Gew.% wässrigen Lösung mit Hilfe des genannten Viskosimeters (Spindel Nr. 1 bzw. 3 / Rotationsgeschwindigkeit 10 rpm) bzw. von 1650 bis 10000 cP, gemessen an einer 1 Gew.% wässrigen Lösung mit Hilfe des genannten Viskosimeters (Spindel Nr. 2 / Rotationsgeschwindigkeit 2 rpm) auf.

[0021] Die Polymeren werden bevorzugt als Pulver eingesetzt. Sie können in Wasser löslich sein.

[0022] Des weiteren können zusätzlich zur Erzielung der notwendigen Bruchfestigkeit der erfindungsgemäßen Darreichungsform mindestens ein natürliches oder synthetisches Wachs (D) mit einer Bruchfestigkeit, gemessen nach der in der vorliegenden Anmeldung offenbarten Methode, von mindestens 500 N eingesetzt werden. Bevorzugt sind die Wachse mit einem Erweichungspunkt von mindestens 60°C. Besonders bevorzugt sind Carnaubawachs und Bienenwachs. Ganz besonders bevorzugt ist Carnaubawachs. Carnaubawachs ist ein natürliches Wachs, das aus den Blättern der Carnaubapalme gewonnen wird und einen Erweichungspunkt von wenigstens  $\geq 80^{\circ}\text{C}$  aufweist. Beim zusätzlichen Einsatz der Wachskomponente wird diese zusammen mit wenigstens einem Polymeren (C) in solchen Mengen eingesetzt, dass die Darreichungsform eine Bruchfestigkeit von mindestens 500 N aufweist.

[0023] Vorzugsweise wird die Komponente (C) in einer Menge von 35 bis 99,9 Gew.%, besonders bevorzugt von wenigstens 50 Gew.%, ganz besonders bevorzugt von wenigstens 60 Gew.%, bezogen auf das Gesamtgewicht der Darreichungsform, eingesetzt.

[0024] Als Hilfsstoffe (B) können die üblichen für die Formulierung von festen Darreichungsformen bekannten Hilfsstoffe verwendet werden. Vorzugsweise sind dies Weichmacher, wie Polyethylenglykol, Hilfsstoffe, die Wirkstofffreisetzung beeinflussend, vorzugsweise hydrophobe oder hydrophile, vorzugsweise hydrophile Polymere, ganz besonders bevorzugt Hydroxypropylcellulose, und/oder Antioxidantien. Als Antioxidantien eignen sich Ascorbinsäure, Butylhydroxyanisol, Butylhydroxytoluol, Salze der Ascorbinsäure, Monothioglycerin, phosphorige Säure, Vitamin C, Vitamin E und dessen Derivate, Natriumbisulfit, besonders bevorzugt Butylhydroxytoluol (BHT) oder Butylhydroxyanisol (BHA) und  $\alpha$ -Tocopherol.

[0025] Das Antioxidanz wird vorzugsweise in Mengen von 0,01 bis 10 Gew.%, vorzugsweise 0,03 bis 5 Gew.%, bezogen auf das Gesamtgewicht der Darreichungsform, eingesetzt.

[0026] Die erfindungsgemäßen Darreichungsformen zeichnen sich dadurch aus, dass sie aufgrund ihrer Härte mit Hilfe von üblichen, einem Missbraucher zur Verfügung stehenden Zerkleinerungsmitteln, wie Mörser und Pistill, nicht zu pulverisieren sind. Ein oraler, parenteraler, insbesondere intravenöser oder nasaler Missbrauch ist dadurch praktisch ausgeschlossen. Um jedoch jeden möglichen Missbrauch der erfindungsgemäßen Darreichungsformen vorzubeugen, können die erfindungsgemäßen Darreichungsformen in einer bevorzugten Ausführungsform als Hilfsstoffe (B) weitere Missbrauchs-erschwerende bzw. -verhindernde Mittel enthalten.

[0027] So kann die erfindungsgemäße, gegen Missbrauch gesicherte Darreichungsform, die neben einem oder mehreren Wirkstoffen mit Missbrauchspotential, mindestens einem härtebildenden Polymer (C) und ggf. mindestens einen Wachs (D) noch wenigstens eine der nachfolgenden Komponenten (a)-(e) als Hilfsstoffe (B) aufweist:

(a) wenigstens einen den Nasen- und/oder Rachenraum reizenden Stoff,

(b) wenigstens ein viskositätserhöhendes Mittel, das in einem mit Hilfe einer notwendigen Mindestmenge an einer wässrigen Flüssigkeit aus der Darreichungsform gewonnenen Extrakt ein Gel bildet, welches vorzugsweise beim Einbringen in eine weitere Menge einer wässrigen Flüssigkeit visuell unterscheidbar bleibt,

(c) wenigstens einen Antagonisten für jeden der Wirkstoffe mit Missbrauchspotential,

(d) wenigstens ein Emetikum.

(e) wenigstens einen Farbstoff als aversives Mittel

(f) wenigstens einen Bitterstoff

[0028] Die Komponenten (a) bis (f) sind jeweils für sich allein zusätzlich zur Sicherung der erfindungsgemäßen Darreichungsform gegen Missbrauch geeignet. So eignet sich die Komponente (a) bevorzugt zur Sicherung gegen nasalen, oralen und/oder parenteralen, vorzugsweise intravenösen, Missbrauch, die Komponente (b) bevorzugt gegen parenteralen, besonders bevorzugt intravenösen und/oder nasalen Missbrauch, die Komponente (c) bevorzugt gegen nasalen und/oder parenteralen, besonders bevorzugt intravenösen, Missbrauch, die Komponente (d) vorzugsweise gegen parenteralen, besonders bevorzugt intravenösen, und/oder oralen und/oder nasalen Missbrauch, die Komponente (e) als visuelles Abschreckungsmittel gegen oralen oder parenteralen Missbrauch und die Komponente (f) gegen oralen oder

nasalen Missbrauch. Durch die erfindungsgemäße Mitverwendung von wenigstens einer der vorstehend genannten Komponenten, gelingt es, bei erfindungsgemäßen Darreichungsformen noch effektiver den Missbrauch zu erschweren.

**[0029]** In einer Ausführungsform kann die erfindungsgemäße Darreichungsform auch zwei oder mehrere der Komponenten (a)-(f) in einer Kombination aufweisen, vorzugsweise (a), (b) und ggf. (c) und/oder (f) und/oder (e) bzw. (a), (b) und ggf. (d) und/oder (f) und/oder (e).

**[0030]** In einer weiteren Ausführungsform kann die erfindungsgemäße Darreichungsform sämtliche Komponenten (a)-(f) aufweisen.

**[0031]** Sofern die erfindungsgemäße Darreichungsform gegen Missbrauch die Komponente (a) umfasst, kommen als den Nasen- und/oder Rachenraum reizende Stoffe erfindungsgemäß sämtliche Stoffe in Betracht, die bei entsprechender Applikation über den Nasen- und/oder Rachenraum eine Reaktion des Körpers hervorrufen, die entweder für den Missbraucher so unangenehm ist, dass er die Applikation nicht weiter fortsetzen will oder kann, z.B. ein Brennen, oder die auf physiologische Art und Weise einer Aufnahme des entsprechenden Wirkstoffes entgegenwirken, z.B. über eine vermehrte nasale Sekretbildung oder Niesen. Diese üblicherweise den Nasen- und/oder Rachenraum reizenden Stoffe können auch bei parenteraler, insbesondere intravenöser, Applikation ein sehr unangenehmes Gefühl bis hin zu unerträglichen Schmerzen verursachen, so daß der Mißbraucher die Einnahme nicht länger fortsetzen will oder kann.

**[0032]** Besonders geeignete, den Nasen- und/oder Rachenraum reizende Stoffe sind solche Stoffe, die ein Brennen, einen Juckreiz, einen Niesreiz, eine vermehrte Sekretbildung oder eine Kombination mindestens zweier dieser Reize verursachen. Entsprechende Stoffe und deren üblicherweise einzusetzenden Mengen sind dem Fachmann an sich bekannt oder können durch einfache Vorversuche ermittelt werden.

**[0033]** Der den Nasen- und/oder Rachenraum reizende Stoff der Komponente (a) basiert vorzugsweise auf einem oder mehreren Inhaltsstoffen oder einem oder mehreren Pflanzenteilen wenigstens einer Scharfstoffdroge.

**[0034]** Entsprechende Scharfstoffdrogen sind dem Fachmann an sich bekannt und werden beispielsweise in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" von Prof. Dr. Hildebert Wagner, 2., bearbeitete Auflage, Gustav Fischer Verlag, Stuttgart-New York, 1982, Seiten 82 ff., beschrieben. Die entsprechende Beschreibung wird hiermit als Referenz eingeführt und gilt als Teil der Offenbarung.

**[0035]** Unter Darreichungseinheit wird eine separate bzw. separierbare Dosiseinheit, wie z. B. eine Tablette oder eine Kapsel, verstanden.

**[0036]** Vorzugsweise kann der erfindungsgemäßen Darreichungsform als Komponente (a) einer oder mehrere Inhaltsstoffe wenigstens einer Scharfstoffdroge, ausgewählt aus der Gruppe bestehend aus *Allii sativi* Bulbus, *Asari* Rhizoma c. *Herba*, *Calami* Rhizoma, *Capsici* Fructus (Paprika), *Capsici* Fructus acer (Cayennepfeffer), *Curcumae* longae Rhizoma, *Curcumae* xanthorrhizae Rhizoma, *Galangae* Rhizoma, *Myristicae* Semen, *Piperis* nigri Fructus (Pfeffer), *Sinapis* albae (Erucae) Semen, *Sinapis* nigri Semen, *Zedoariae* Rhizoma und *Zingiberis* Rhizoma, besonders bevorzugt aus der Gruppe bestehend aus *Capsici* Fructus (Paprika), *Capsici* Fructus acer (Cayennepfeffer) und *Piperis* nigri Fructus (Pfeffer), hinzugefügt werden.

**[0037]** Bei den Inhaltsstoffen der Scharfstoffdrogen handelt es sich bevorzugt um o-Methoxy(Methyl)-phenol-Verbindungen, Säureamid-Verbindungen, Senföle oder Sulfidverbindungen oder um davon abgeleiteten Verbindungen.

**[0038]** Besonders bevorzugt ist wenigstens ein Inhaltsstoff der Scharfstoffdrogen ausgewählt aus der Gruppe bestehend aus Myristicin, Elemicin, Isoeugenol,  $\alpha$ -Asaron, Safrol, Gingerolen, Xanthorrhizol, Capsaicinoiden, vorzugsweise Capsaicin, Capsaicin- Derivate, wie N-vanillyl -9E-octadecenamid, Dihydrocapsaicin, Nordihydrocapsaicin, Homocapsaicin, Norcapsaicin, und Nomorcapsaicin, Piperin, vorzugsweise trans-Piperin, Glucosinolaten, vorzugsweise auf Basis von nichtflüchtigen Senfölen, besonders bevorzugt auf Basis von p-Hydroxybenzylsenfö, Methylmercaptosenfö oder Methylsulfonylsenfö, und von diesen Inhaltsstoffen abgeleiteten Verbindungen.

**[0039]** Vorzugsweise kann die erfindungsgemäße Darreichungsform die Pflanzenteile der entsprechenden Scharfstoffdrogen in einer Menge von 0,01 bis 30 Gew.-%, besonders bevorzugt 0,1 bis 0,5 Gew.-%, jeweils bezogen auf das Gesamtgewicht der Darreichungseinheit, enthalten.

Kommen ein oder mehrere Inhaltsstoffe entsprechender Scharfstoffdrogen zum Einsatz, beträgt deren Menge in einer erfindungsgemäßen Darreichungseinheit bevorzugt 0,001 bis 0,005 Gew.-%, bezogen auf das Gesamtgewicht der Darreichungseinheit.

**[0040]** Eine weitere Möglichkeit bei der erfindungsgemäßen Darreichungsform gegen Missbrauch vorzubeugen, besteht darin, wenigstens ein viskositätserhöhendes Mittel als weitere Missbrauchs-verhindernde Komponente (b) der Darreichungsform zuzusetzen, das in einem mit Hilfe einer notwendigen Mindestmenge an einer wässrigen Flüssigkeit, vorzugsweise als ein aus der Darreichungsform gewonnenes wässriges Extrakt, ein Gel bildet, das kaum gefahrlos applizierbar ist und vorzugsweise beim Einbringen in eine weitere Menge einer wässrigen Flüssigkeit visuell unterscheidbar bleibt.

**[0041]** Visuelle Unterscheidbarkeit im Sinne der vorliegenden Erfindung bedeutet, dass das mit Hilfe einer notwendigen Mindestmenge an wässriger Flüssigkeit gebildete, Wirkstoff-haltige Gel beim Einbringen vorzugsweise mit Hilfe einer Injektionsnadel, in eine weitere Menge wäßriger Flüssigkeit von 37°C im wesentlichen unlöslich und zusammenhängend bleibt und nicht auf einfache Weise so dispergiert werden kann, dass eine parenterale, insbesondere intravenöse,

gefahrlose Applikation möglich ist. Vorzugsweise beträgt die Dauer der visuellen Unterscheidbarkeit wenigstens eine Minute, vorzugsweise mindestens 10 Minuten.

[0042] Die Viskositätssteigerung des Extrakts führt dazu, dass dessen Nadelgängigkeit bzw. Spritzbarkeit erschwert oder sogar unmöglich gemacht wird. Sofern das Gel visuell unterscheidbar bleibt, bedeutet dies, dass das erhaltene Gel beim Einbringen in eine weitere Menge wässriger Flüssigkeit, z.B. durch Einspritzen in Blut, zunächst in Form eines weitgehend zusammenhängenden Fadens erhalten bleibt, der zwar durch mechanische Einwirkung in kleinere Bruchstücke zerteilt, nicht aber so dispergiert oder sogar gelöst werden kann, daß eine parenterale, insbesondere intravenöse, Applikation gefahrlos möglich ist. In Kombination mit mindestens einer ggf. vorhandenen Komponente (a) bis (e) führt dies zusätzlich zu unangenehmen Brennen, Erbrechen, schlechtem Geschmack und/oder zur visuellen Abschreckung.

[0043] Eine intravenöse Applikation eines entsprechenden Gels würde daher mit großer Wahrscheinlichkeit zur Verstopfung von Gefäßen, verbunden mit schweren gesundheitlichen Schäden des Missbrauchers führen.

[0044] Zur Überprüfung, ob ein viskositätssteigerndes Mittel als Komponente (b) zur Anwendung in der erfindungsgemäßen Darreichungsform geeignet ist, wird der Wirkstoff mit dem viskositätssteigernden Mittel gemischt und in 10 ml Wasser bei einer Temperatur von 25 °C suspendiert. Bildet sich hierbei ein Gel, welches den obenstehend genannten Bedingungen genügt, eignet sich das entsprechende viskositätssteigernde Mittel zur zusätzlichen Missbrauchs-Vorbeugung bzw. -Verhinderung bei den erfindungsgemäßen Darreichungsformen.

[0045] Sofern der erfindungsgemäßen Darreichungsform die Komponente (b) hinzugefügt wird, kommen vorzugsweise eine oder mehrere viskositätssteigernde Mittel zum Einsatz, die ausgewählt sind aus der Gruppe umfassend mikrokristalline Cellulose mit 11 Gew.-% Carboxymethylcellulose-Natrium (Avicel® RC 591), Carboxymethylcellulose-Natrium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), Polyacrylsäure (Carbopol® 980 NF, Carbopol® 981), Johannisbrotkernmehl (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), Pektine, vorzugsweise aus Citrusfrüchten oder Äpfeln (Cesapectin® HM Medium Rapid Set), Wachsmasstärke (C\*Gel 04201®), Natriumalginat (Frimulsion ALG (E401)®), Guarkernmehl (Frimulsion BM®, Polygum 26/1-75®), Iota-Carrageen (Frimulsion D021®), Karaya Gummi, Gellangummi (Kelcogel F®, Kelcogel LT100®), Galaktomannan (Meyprogat 150®), Tarakernmehl (Polygum 43/1®), Propylenglykoalginat (Protanal-Ester SD-LB®),

[0046] Natrium-Hyaluronat, Tragant, Taragummi (Vidogum SP 200®), fermentiertes Polysaccharid- Wulan Gum (K1A96), Xanthan-Gummi (Xantural 180®). Xanthane sind besonders bevorzugt. Die in Klammern angegebenen Bezeichnungen sind die Handelsnamen, unter denen die jeweiligen Materialien am Markt geführt sind. Im allgemeinen ist eine Menge von 0,1 bis 20 Gew.%, besonders bevorzugt 0,1 bis 15 Gew.%, bezogen auf das Gesamtgewicht der Darreichungsform, der/des genannten viskositätssteigernden Mittels ausreichend, um die vorstehend genannten Bedingungen zu erfüllen.

[0047] Die viskositätssteigernden Mittel der Komponente (b), sofern vorgesehen, liegen in der erfindungsgemäßen Darreichungsform bevorzugt in Mengen von  $\geq 5$  mg pro Darreichungseinheit, d.h. pro Dosiereinheit vor.

[0048] In einer besonders bevorzugten Ausführungsform der vorliegenden Erfindung kommen als Komponente (b) solche viskositätssteigernden Mittel zum Einsatz, die bei der Extraktion aus der Darreichungsform mit der notwendigen Mindestmenge an wässriger Flüssigkeit ein Gel bilden, das Luftblasen einschließt. Die so erhaltenen Gele zeichnen sich durch ein trübes Erscheinungsbild aus, durch das der potentielle Missbraucher zusätzlich optisch gewarnt und von dessen parenteraler Applikation abgehalten wird.

[0049] Die Komponente (c) kann auch gegebenenfalls als zusätzliches viskositätssteigerndes Mittel dienen, das mit Hilfe einer notwendigen Mindestmenge einer wässrigen Flüssigkeit, ein Gel bildet.

[0050] Es ist auch möglich, die viskositätssteigernden Mittel und die übrigen Bestandteile in räumlich voneinander getrennter Anordnung in der erfindungsgemäßen Darreichungsform zu formulieren.

[0051] Des weiteren kann die erfindungsgemäße Darreichungsform zur Vorbeugung und Sicherung gegen Missbrauch die Komponente (c) aufweisen, nämlich einen oder mehrere Antagonisten für den Wirkstoff bzw. die Wirkstoffe mit Missbrauchspotential, wobei die Antagonistenmenge vorzugsweise räumlich getrennt von den übrigen Bestandteilen der erfindungsgemäßen Darreichungsform vorliegen und keine Wirkung bei bestimmungsgemäßer Verwendung entfalten.

[0052] Geeignete Antagonisten zur Verhinderung des Mißbrauchs der Wirkstoffe sind dem Fachmann an sich bekannt und können als solche oder in Form entsprechender Derivate, insbesondere Ester oder Ether, oder jeweils in Form entsprechender physiologisch verträglicher Verbindungen, insbesondere in Form ihrer Salze oder Solvate in der erfindungsgemäßen Darreichungsform vorliegen.

[0053] Sofern der in der Darreichungsform vorliegende Wirkstoff ein Opioid ist, kommt als Antagonist bevorzugt ein Antagonist ausgewählt aus der Gruppe umfassend Naloxon, Naltrexon, Nalmefen, Nalid, Nalmexon, Nalorphin oder Naluphin, jeweils ggf. in Form einer entsprechenden physiologisch verträglichen Verbindung, insbesondere in Form einer Base, eines Salzes oder Solvates, zum Einsatz. Vorzugsweise werden die entsprechenden Antagonisten, sofern eine Ausrüstung mit der Komponente (c) vorgesehen ist, in einer Menge von  $\geq 1$  mg, besonders bevorzugt in einer Menge von 3 bis 100 mg, ganz besonders bevorzugt in einer Menge von 5 bis 50 mg auf pro Darreichungsform, d.h. pro Dosiereinheit eingesetzt.



**[0054]** Weist die erfindungsgemäße Darreichungsform als Wirkstoff ein Stimulanz auf, ist der Antagonist bevorzugt ein Neuroleptikum, vorzugsweise wenigstens eine Verbindung ausgewählt aus der Gruppe bestehend aus Haloperidol, Promethacin, Fluophenozin, Perphenazin, Levomepromazin, Thioridazin, Perazin, Chlorpromazin, Chlorprothexin, Zucklopantexol, Flupentexol, Prithipendyl, Zotepin, Penperidol, Piparmeron, Melperol und Bromperidol.

**[0055]** Vorzugsweise weist die erfindungsgemäße Darreichungsform diese Antagonisten in einer üblichen, dem Fachmann bekannten therapeutischen Dosierung, besonders bevorzugt in einer gegenüber der üblichen Dosierung verdoppelten bis verdreifachten Menge pro Dosiereinheit auf.

**[0056]** Sofern die Kombination zur Vorbeugung und Sicherung der erfindungsgemäßen Darreichungsform gegen Mißbrauch die Komponente (d) umfaßt, kann sie wenigstens ein Emetikum aufweisen, das vorzugsweise in einer räumlich getrennten Anordnung von den übrigen Komponenten der erfindungsgemäßen Darreichungsform vorliegen und bei bestimmungsgemäßer Anwendung keine Wirkung im Körper entfalten sollte.

**[0057]** Geeignete Emetika zur Verhinderung des Missbrauchs eines Wirkstoffs sind dem Fachmann an sich bekannt und können als solche oder in Form entsprechender Derivate, insbesondere Ester oder Ether, oder jeweils in Form entsprechender physiologisch verträglicher Verbindungen, insbesondere in Form ihrer Salze oder Solvate in der erfindungsgemäßen Darreichungsform vorliegen.

**[0058]** In der erfindungsgemäßen Darreichungsform kann bevorzugt ein Emetikum auf Basis eines oder mehrerer Inhaltsstoffe von *Radix Ipecacuanhae* (Brechwurzel), vorzugsweise auf Basis des Inhaltsstoffes Emetin, in Betracht, wie sie z.B. in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" von Prof. Dr. Hildebert Wagner, 2., bearbeitete Auflage, Gustav Fischer Verlag, Stuttgart, New York 1982 beschrieben werden. Die entsprechende Literaturbeschreibung wird hiermit als Referenz eingeführt und gilt als Teil der Offenbarung.

**[0059]** Vorzugsweise kann die erfindungsgemäße Darreichungsform als Komponente (d) das Emetikum Emetin aufweisen, bevorzugt in einer Menge von  $\geq 3$  mg, besonders bevorzugt  $\geq 10$  mg und ganz besonders bevorzugt in einer Menge von  $\geq 20$  mg pro Darreichungsform, d.h. Dosiereinheit.

**[0060]** Ebenfalls bevorzugt kann als Emetikum Apomorphin in der erfindungsgemäßen Missbrauchssicherung zum Einsatz kommen, vorzugsweise in einer Menge von vorzugsweise  $\geq 3$  mg, besonders bevorzugt  $\geq 5$  mg und ganz besonders bevorzugt  $\geq 7$  mg pro Dosiereinheit.

**[0061]** Sofern die erfindungsgemäße Darreichungsform die Komponente (e) als weiteren missbrauchsverhindernden Hilfsstoff enthält, so wird durch den Einsatz eines solchen Farbstoffes, insbesondere bei dem Versuch, den Wirkstoff für eine parenterale, vorzugsweise intravenöse Applikation, zu extrahieren, eine intensive Farbgebung einer entsprechenden wässrigen Lösung hervorgerufen, die zur Abschreckung beim potentiellen Missbraucher führen kann. Auch ein oraler Missbrauch, der üblicherweise über eine wässrige Extraktion des Wirkstoffes eingeleitet wird, kann durch diese Farbgebung verhindert werden. Geeignete Farbstoffe sowie die für die notwendige Abschreckungswirkung erforderlichen Mengen sind der WO 03/015531 zu entnehmen, wobei die entsprechende Offenbarung als Teil der vorliegenden Offenbarung gelten soll und hiermit als Referenz eingeführt wird.

**[0062]** Sofern die erfindungsgemäße Darreichungsform als zusätzlichen Missbrauchsverhindernden Hilfsstoff die Komponente (f) enthält, so wird durch diesen Zusatz von wenigstens einem Bitterstoff durch die damit eintretende Geschmacksverschlechterung der Darreichungsform der orale und/oder nasale Missbrauch zusätzlich verhindert.

**[0063]** Geeignete Bitterstoffe sowie die für den Einsatz wirksamen Mengen sind der US-2003/0064099 A1 zu entnehmen, deren entsprechende Offenbarung als Offenbarung der vorliegenden Anmeldung gelten soll und hiermit als Referenz eingeführt wird. Vorzugsweise eignen sich als Bitterstoffe Aromaöle, vorzugsweise Pfefferminzöl, Eukalyptusöl, Bittermandelöl, Menthol, Fruchtaromastoffe, vorzugsweise Aromastoffe von Zitronen, Orangen, Limonen, Grapefruit oder Mischungen davon, und/oder Denatonium-Benzozat (Bitrex®). Besonders bevorzugt ist Denatonium-Benzozat.

**[0064]** Die erfindungsgemäße feste Darreichungsform eignet sich zur oralen, vaginalen oder rektalen, vorzugsweise zur oralen Einnahme. Vorzugsweise ist sie nicht filmförmig.

**[0065]** Die erfindungsgemäße Darreichungsform kann in multipartikulärer Form, bevorzugt in Form von Mikrotabletten, Mikrokapseln, Mikropellets, Granulaten, Sphäroiden, Perlen oder Pellets, ggf. in Kapseln abgefüllt oder zu Tabletten verpreßt, vorzugsweise zur oralen Verabreichung, vorliegen. Vorzugsweise weisen die multipartikulären Formen eine Größe bzw. Größenverteilung im Bereich von 0,1 bis 3 mm, besonders bevorzugt im Bereich von 0,5 bis 2 mm auf. Je nach gewünschter Darreichungsform werden ggf. auch die üblichen Hilfsstoffe (B) zur Formulierung der Darreichungsform mitverwendet.

Die erfindungsgemäß gegen Missbrauch gesicherte, feste Darreichungsform wird vorzugsweise ohne Extruder-Einsatz hergestellt, indem vorzugsweise die Komponenten (A), (B), (C) und die ggf. vorhandene Komponente (D) sowie ggf. mindestens eine der ggf. vorhandenen weiteren missbrauchsverhindernden Komponenten (a) - (f) mitgemischt oder, wenn notwendig, separat unter Zugabe der Komponente (C) und gegebenenfalls der Komponente (D) gemischt werden und die resultierende Mischung bzw. die resultierenden Mischungen ggf. nach einer Granulierung zu der Darreichungsform unter vorangehender oder gleichzeitiger Wärmeeinwirkung durch Krafteinwirkung geformt wird bzw. werden.

**[0066]** Diese Erwärmung und Krafteinwirkung zur Herstellung der Darreichungsform erfolgt ohne Extruder-Einsatz.

**[0067]** Die Mischung der Komponenten (A), (B), (C) und ggf. (D) sowie bzw. der ggf. vorhandenen weiteren Kompo-

nennten (a) - (f) und ggf. der Komponenten (C) und der ggf. vorhandenen Komponente (D) erfolgt ggf. jeweils in einem dem Fachmann bekannten Mischgerät. Das Mischgerät kann beispielsweise ein Wälzmischer, Schüttelmischer, Schermischer oder Zwangsmischer sein.

**[0068]** Die resultierende Mischung bzw. die resultierenden Mischungen wird (werden) vorzugsweise direkt zu der erfindungsgemäßen Darreichungsform unter vorangehender oder gleichzeitiger Wärmeeinwirkung durch Krafteinwirkung geformt. Beispielsweise kann die Mischung durch Direkttablettierung zu Tabletten geformt werden. Bei einer Direkttablettierung unter gleichzeitiger Wärmeeinwirkung wird mit Hilfe des Tablettierwerkzeugs, d. h. des Unterstempels, Oberstempels und der Matrize die zu verpressende Mischung zumindest bis zum Erweichungspunkt der Polymeren-Komponente (C) erhitzt und dabei verpresst. Bei einer Direkttablettierung unter vorangehender Wärmeeinwirkung wird das zu verpressende Gut unmittelbar vor der Tablettierung mindest bis zur Erweichungstemperatur der Komponente (C) erhitzt und anschließend mit Hilfe des Tablettierwerkzeugs verpresst.

**[0069]** Die resultierende Mischung aus den Komponenten (A), (B), (C) und ggf. der Komponente (D) sowie der ggf. vorhandenen Komponenten (a) bis (f) bzw. der Mischung mindestens einer dieser Komponenten (a) bis (f) mit der Komponente (C) kann auch zuerst granuliert und anschließend unter vorangehender oder gleichzeitiger Wärmeeinwirkung unter Krafteinwirkung zu der erfindungsgemäßen Darreichungsform geformt werden.

**[0070]** Bei jeder Krafteinwirkung erfolgt diese solange, bis die Darreichungsform eine Bruchhärte von mindestens 500 N erreicht hat.

**[0071]** Die Granulierung kann durch Feuchtgranulation oder Schmelzgranulation in bekannten Granulatoren durchgeführt werden.

**[0072]** Jede der erwähnten Verfahrensschritte, insbesondere die Erwärmungen und gleichzeitige oder nachfolgende Krafteinwirkung zur Herstellung der erfindungsgemäßen Darreichungsform erfolgt ohne Extruder-Einsatz.

**[0073]** In einer weiteren bevorzugten Ausführungsform liegt die erfindungsgemäße Darreichungsform in Form einer Tablette, einer Kapsel oder in Form eines oralen osmotischen therapeutischen Systems (OROS) vor, vorzugsweise wenn mindestens noch eine weitere missbrauchsverhindernde Komponente (a) - (f) vorhanden ist.

**[0074]** Sofern die Komponenten (c) und/oder (d) und/oder (f) in der erfindungsgemäßen Darreichungsform vorhanden sind, ist darauf zu achten, dass sie so formuliert oder so gering dosiert sind, daß sie bei bestimmungsgemäßer Applikation der Darreichungsform praktisch keine den Patienten oder die Wirksamkeit des Wirkstoffs beeinträchtigende Wirkung entfalten können.

**[0075]** Wenn die erfindungsgemäße Darreichungsform die Komponente (d) und/oder (f) enthält, ist die Dosierung so zu wählen, dass bei bestimmungsgemäßer oraler Applikation keine negative Wirkung hervorgerufen wird. Wird jedoch die vorgesehene Dosierung bei einem Missbrauch überschritten, wird Übelkeit bzw. Brechreiz bzw. schlechter Geschmack hervorgerufen. Die jeweilige Menge der Komponente (d) und/oder (f), die vom Patienten bei bestimmungsgemäßer oraler Applikation noch toleriert wird, kann vom Fachmann durch einfache Vorversuche ermittelt werden.

**[0076]** Sofern aber unabhängig von der praktisch nicht möglichen Pulverisierbarkeit der erfindungsgemäßen Darreichungsform zur Sicherung der Darreichungsform der Einsatz der Komponenten (c) und/oder (d) und/oder (f) vorgesehen ist, sollten diese Komponenten bevorzugt in einer so hohen Dosierung zum Einsatz kommen, dass sie bei einer missbräuchlichen Applikation der Darreichungsform eine intensive negative Wirkung beim Missbraucher hervorrufen. Dies gelingt vorzugsweise durch eine räumliche Trennung zumindest des Wirkstoffes bzw. der Wirkstoffe von den Komponenten (c) und/oder (d) und/oder (f), wobei bevorzugt der Wirkstoff bzw. die Wirkstoffe in wenigstens einer Untereinheit (X) und die Komponenten (c) und/oder (d) und/oder (f) in wenigstens einer Untereinheit (Y) vorliegen, und wobei die Komponenten (c), (d) und (f) bei bestimmungsgemäßer Applikation der Darreichungsform bei Einnahme und/oder im Körper nicht ihre Wirkung entfalten und die übrigen Formulierungskomponenten insbesondere die Komponente (C) und ggf. (D) identisch sind.

**[0077]** Sofern die erfindungsgemäße Darreichungsform wenigstens 2 der Komponenten (c) und (d) bzw. (f) aufweist, können diese jeweils in derselben oder in verschiedenen Untereinheiten (Y) vorliegen. Vorzugsweise liegen, sofern vorhanden, alle Komponenten (c) und (d) und (f) in ein- und derselben Untereinheit (Y) vor.

**[0078]** Untereinheiten im Sinne der vorliegenden Erfindung sind feste Formulierungen, die jeweils neben üblichen, dem Fachmann bekannten Hilfsstoffen den (die) Wirkstoff(e), mindestens ein Polymer (C) und die gegebenenfalls vorhandene Komponente (D) und gegebenenfalls wenigstens eine der gegebenenfalls vorhandenen Komponenten (a) und/oder (b) und/oder (e) bzw. jeweils wenigstens ein Polymer (C) und gegebenenfalls (D) und den (die) Antagonist(en) und/oder das Emetikum (die Emetika) und/oder die Komponente (e) und/oder die Komponente (f) und gegebenenfalls wenigstens eine der gegebenenfalls vorhandenen Komponenten (a) und/oder (b) enthalten. Dabei ist darauf zu achten, dass jede der genannten Untereinheiten nach den vorstehend angegebenen Verfahren formuliert werden.

**[0079]** Ein wesentlicher Vorteil der getrennten Formulierung der Wirkstoffe von den Komponenten (c) bzw. (d) bzw. (f) in Untereinheiten (X) und (Y) der erfindungsgemäßen Darreichungsform besteht darin, dass bei ihrer bestimmungsgemäßen Applikation die Komponenten (c) und/oder (d) und/oder (f) bei Einnahme und/oder im Körper praktisch nicht freigesetzt werden oder nur in so geringen Mengen freigesetzt werden, dass sie keine den Patienten oder den Therapieerfolg beeinträchtigende Wirkung entfalten oder bei der Passage durch den Körper des Patienten nur an solchen

Freisetzungsorten abgegeben werden, an denen eine für ihre Wirksamkeit ausreichende Resorption nicht gegeben ist. Vorzugsweise werden die Komponenten (c) und/oder (d) und/oder (f) bei bestimmungsgemäßer Applikation der Darreichungsform im Körper des Patienten praktisch nicht freigesetzt oder vom Patienten nicht wahrgenommen.

**[0080]** Der Fachmann versteht, dass diese vorstehend genannten Bedingungen in Abhängigkeit von den jeweils eingesetzten Komponenten (c), (d) und/oder (f) sowie der Formulierung der Untereinheiten bzw. der Darreichungsform variieren können. Die für die jeweilige Darreichungsform optimale Formulierung kann durch einfache Vorversuche ermittelt werden. Entscheidend ist, dass die jeweiligen Untereinheiten das Polymer (C) und gegebenenfalls die Komponente (D) enthalten und in der vorstehend angegebenen Weise formuliert wurden.

**[0081]** Sollte es den Missbrauchern wider Erwarten gelingen, eine solche erfindungsgemäße Darreichungsform, welche die Komponenten (c) und/oder (e) und/oder (d) und/oder (f) in Untereinheiten (Y) aufweist, zum Zwecke der mißbräuchlichen Einnahme des Wirkstoffes zu zerkleinern und ein Pulver zu erhalten, das mit einem geeigneten Extraktionsmittel extrahiert wird, wird neben dem Wirkstoff auch die jeweilige Komponente (c) und/oder (e) und/oder (f) und/oder (d) in einer Form erhalten, in der sie von dem Wirkstoff nicht auf einfache Weise zu separieren ist, so dass sie bei der Applikation der manipulierten Darreichungsform, insbesondere bei oraler und/oder parenteraler Verabreichung, ihre Wirkung bei Einnahme und/oder im Körper entfaltet und zusätzlich eine der Komponente (c) und/oder (d) und/oder (f) entsprechende negative Wirkung beim Missbraucher hervorruft oder ein Versuch, den Wirkstoff zu extrahieren durch die Farbgebung abschreckt und so den Missbrauch der Darreichungsform verhindert.

**[0082]** Die Formulierung einer erfindungsgemäßen Darreichungsform, in der eine räumliche Trennung des Wirkstoffes bzw. der Wirkstoffe von den Komponenten (c), (d) und/oder (e), vorzugsweise durch Formulierung in verschiedenen Untereinheiten erfolgt ist, kann in vielfältiger Art und Weise erfolgen, wobei die entsprechenden Untereinheiten in der erfindungsgemäßen Darreichungsform jeweils in beliebiger räumlicher Anordnung zueinander vorliegen können, sofern die vorstehend genannten Bedingungen für die Freisetzung der Komponenten (c) und/oder (d) erfüllt sind.

**[0083]** Der Fachmann versteht, dass die ggf. auch vorliegenden Komponente(n) (a) und/oder (b) bevorzugt sowohl in den jeweiligen Untereinheiten (X) und (Y) als auch in Form von eigenständigen, den Untereinheiten (X) und (Y) entsprechenden Untereinheiten in der erfindungsgemäßen Darreichungsform formuliert werden können, so lange die Sicherung der Darreichungsform gegen den Missbrauch wie auch die Wirkstofffreisetzung bei bestimmungsgemäßer Applikation durch die Art der Formulierung nicht beeinträchtigt werden und das Polymer (C) und gegebenenfalls (D) mit formuliert und die Formulierung gemäß den vorstehend angegebenen Verfahren zur Erzielung der notwendigen Härte durchgeführt wird.

**[0084]** In einer bevorzugten Ausführungsform der erfindungsgemäßen Darreichungsform liegen die Untereinheiten (X) und (Y) in multipartikulärer Form vor, wobei Mikrotabletten, Mikrokapseln, Mikropellets, Granulaten, Sphäroiden, Perlen oder Pellets bevorzugt sind und sowohl für die Untereinheit (X) als auch (Y) dieselbe Form, d.h. Gestaltung gewählt wird, damit keine Separierung der Untereinheiten (X) von (Y), z. B. durch mechanische Auslese, möglich ist. Die multipartikulären Formen weisen bevorzugt eine Größe im Bereich von 0,1 bis 3 mm, vorzugsweise 0,5 bis 2 mm auf.

**[0085]** Die Untereinheiten (X) und (Y) in multipartikulärer Form können auch bevorzugt in eine Kapsel abgefüllt oder zu einer Tablette verpreßt werden, wobei die jeweiligen Endformulierungen dergestalt erfolgen, dass die Untereinheiten (X) und (Y) auch in der resultierenden Darreichungsform erhalten bleiben.

**[0086]** Die jeweiligen multipartikulären Untereinheiten (X) bzw. (Y) mit identischer Formgebung sollten auch nicht visuell voneinander unterscheidbar sein, damit sie vom Missbraucher nicht durch einfaches Sortieren voneinander separiert werden können. Dies kann beispielsweise durch das Aufbringen identischer Überzüge gewährleistet werden, die neben dieser Egalisierungsfunktion auch weitere Funktionen übernehmen können, wie z.B. die Retardierung eines oder mehrerer Wirkstoffe oder eine magensaftresistente Ausrüstung der jeweiligen Untereinheiten.

**[0087]** Die multipartikulären Untereinheiten können auch als Slurry oder als Suspension in pharmazeutisch unbedenklichen Suspensionsmedien als orale Darreichungsform formuliert werden.

**[0088]** In einer weiteren bevorzugten Ausführungsform der vorliegenden Erfindung sind die Untereinheiten (X) und (Y) jeweils schichtförmig zueinander angeordnet.

**[0089]** Bevorzugt sind hierfür die schichtförmigen Untereinheiten (X) und (Y) in der erfindungsgemäßen Darreichungsform vertikal oder horizontal zueinander angeordnet, wobei jeweils auch eine oder mehrere schichtförmige Untereinheiten (X) und eine oder mehrere schichtförmige Untereinheiten (Y) in der Darreichungsform vorliegen können, so daß neben den bevorzugten Schichtenfolgen (X)-(Y) bzw. (X)-(Y)-(X) beliebige andere Schichtenfolgen in Betracht kommen, ggf. in Kombination mit Schichten enthaltend die Komponenten (a) und/oder (b).

**[0090]** Ebenfalls bevorzugt ist eine erfindungsgemäße Darreichungsform, in der die Untereinheit (Y) einen Kern bildet, der von der Untereinheit (X) vollständig umhüllt wird, wobei zwischen diesen Schichten eine Trennschicht (Z) vorhanden sein kann. Ein entsprechender Aufbau eignet sich bevorzugt auch für die vorstehend genannten multipartikulären Formen, wobei dann beide Untereinheiten (X) und (Y) sowie eine ggf. vorhandene Trennschicht (Z), die der erfindungsgemäßen Härteanforderung genügen muss, in ein- und derselben multipartikulären Form formuliert sind. In einer weiteren bevorzugten Ausführungsform der erfindungsgemäßen Darreichungsform bildet die Untereinheit (X) einen Kern, der von der Untereinheit (Y) umhüllt wird, wobei letztere wenigstens einen Kanal aufweist, der von dem Kern an die Oberfläche

der Darreichungsform führt.

**[0091]** Zwischen einer Schicht der Untereinheit (X) und einer Schicht der Untereinheit (Y) kann die erfindungsgemäße Darreichungsform jeweils eine oder mehrere, vorzugsweise eine, ggf. quellbare Trennschicht (Z) zur räumlichen Trennung der Untereinheit (X) von (Y) aufweisen.

**[0092]** Sofern die erfindungsgemäße Darreichungsform die schichtförmigen Untereinheiten (X) und (Y) sowie eine ggf. vorhandene Trennschicht (Z) in einer zumindest teilweise vertikalen oder horizontalen Anordnung aufweist, liegt sie bevorzugt in Form einer Tablette oder eines Laminats vor.

**[0093]** Hierbei kann in einer besonders bevorzugten Ausführungsform die freie Oberfläche der Untereinheit (Y) vollständig und ggf. zumindest ein Teil der freien Oberfläche der Untereinheit(en) (X) und ggf. zumindest ein Teil der freien Oberfläche der ggf. vorhandenen Trennschicht(en) (Z) mit wenigstens einer die Freisetzung der Komponente (c) und/oder (e) und/oder (d) und/oder (f) verhindernden Barrierschicht (Z') überzogen sein. Auch die Barrierschicht (Z') muss die erfindungsgemäßen Härtevoraussetzungen erfüllen.

**[0094]** Ebenfalls besonders bevorzugt ist eine Ausführungsform der erfindungsgemäßen Darreichungsform, die eine vertikale oder horizontale Anordnung der Schichten der Untereinheiten (X) und (Y) und wenigstens eine dazwischen angeordnete Push-Schicht (p) sowie ggf. eine Trennschicht (Z) aufweist, in der sämtliche freie Oberflächen des aus den Untereinheiten (X) und (Y), der Push-Schicht und der ggf. vorhandenen Trennschicht (Z) bestehenden Schichtaufbaus mit einem semipermeablen Überzug (E) ausgerüstet sind, der für ein Freisetzungsmittel, d.h. üblicherweise eine physiologische Flüssigkeit, durchlässig, für den Wirkstoff und für die Komponente (c) und/oder (d) und/oder (f) im wesentlichen undurchlässig ist, und wobei dieser Überzug (E) im Bereich der Untereinheit (X) wenigstens eine Öffnung zur Freisetzung des Wirkstoffes aufweist.

**[0095]** Eine entsprechende Darreichungsform ist dem Fachmann beispielsweise unter der Bezeichnung orales osmotisches therapeutisches System (OROS), ebenso wie geeignete Materialien und Verfahren zu dessen Herstellung, u.a. aus US 4,612,008, US 4,765,989 und US 4,783,337 bekannt. Die entsprechenden Beschreibungen werden hiermit als Referenz eingeführt und gelten als Teil der Offenbarung.

**[0096]** In einer weiteren bevorzugten Ausführungsform hat die Untereinheit (X) der erfindungsgemäßen Darreichungsform die Form einer Tablette, deren Steg und ggf. eine der beiden Grundflächen mit einer die Komponente (c) und/oder (d) und/oder (f) enthaltenden Barrierschicht (Z') bedeckt ist.

**[0097]** Der Fachmann versteht, dass die bei der Formulierung der erfindungsgemäßen Darreichungsform jeweils zum Einsatz kommenden Hilfsstoffe der Untereinheit(en) (X) bzw. (Y) sowie ggf. der vorhandenen Trennschicht(en) (Z) und/oder der Barrierschicht(en) (Z') in Abhängigkeit von deren Anordnung in der erfindungsgemäßen Darreichungsform, der Applikationsart sowie in Abhängigkeit von dem jeweiligen Wirkstoff der ggf. vorhandenen Komponenten (a) und/oder (b) und/oder (e) und der Komponente (c) und/oder (d) und/oder (f) variieren. Die Materialien, die über die jeweils erforderlichen Eigenschaften verfügen sind, dem Fachmann an sich bekannt.

**[0098]** Sofern die Freisetzung der Komponente (c) und/oder (d) und/oder (f) aus der Untereinheit (Y) der erfindungsgemäßen Darreichungsform mit Hilfe einer Umhüllung, vorzugsweise einer Barrierschicht, verhindert wird, kann die Untereinheit aus üblichen, dem Fachmann bekannten Materialien bestehen, sofern sie wenigstens ein Polymer (C) und gegebenenfalls (D) zur Erfüllung der Härtebedingung der erfindungsgemäßen Darreichungsform enthält.

**[0099]** Ist eine entsprechende Barrierschicht (Z') zur Verhinderung der Freisetzung der Komponente (c) und/oder (d) und/oder (f) nicht vorgesehen, sind die Materialien der Untereinheiten so zu wählen, dass eine Freisetzung der jeweiligen Komponente (c) und/oder (d) aus der Untereinheit (Y) praktisch ausgeschlossen ist. Bevorzugt können hierzu die nachstehend aufgeführten Materialien zum Einsatz kommen, die auch für den Aufbau der Barrierschicht geeignet sind.

**[0100]** Bevorzugte Materialien sind solche, die ausgewählt sind aus der Gruppe umfassend Alkylcellulosen, Hydroxyalkylcellulosen, Glucanen, Skleroglucanen, Mannanen, Xanthanen, Copolymeren aus Poly[bis(p-carboxyphenoxy)propan und Sebacinsäure, vorzugsweise in einem Molverhältnis von 20:80 (unter der Bezeichnung Polifeprosan 20® am Markt geführt), Carboxymethylcellulosen, Celluloseethern, Celluloseestern, Nitrocellulosen, Polymeren auf Basis von (Meth)acrylsäure sowie deren Estern, Polyamiden, Polycarbonaten, Polyalkylenen, Polyalkylenglykolen, Polyalkylenoxiden, Polyalkylenterephthalate, Polyvinylalkohole, Polyvinylether, Polyvinylester, halogenierte Polyvinyle, Polyglykole, Polysiloxane sowie Polyurethane und deren Copolymeren.

**[0101]** Besonders geeignete Materialien können ausgewählt werden aus der Gruppe umfassend Methylcellulose, Ethylcellulose, Hydroxypropylmethylcellulose, Hydroxybutylmethylcellulose, Celluloseacetat, Cellulosepropionat (von niederem, mittlerem oder erhöhtem Molekulargewicht), Celluloseacetatpropionat, Celluloseacetatbutyrat, Celluloseacetatphtalat, Carboxymethylcellulose, Cellulosetriacetat, Natrium-Cellulosesulfat, Polymethylmethacrylat, Polyethylmethacrylat, Polybutylmethacrylat, Polyisobutylmethacrylat, Polyhexylmethacrylat, Polyisodecylmethacrylat, Polyaurylmethacrylat, Polyphenylmethacrylat, Polymethylacrylat, Polyisopropylacrylat, Polyisobutylacrylat, Polyoctadecylacrylat, Polyethylen, Polyethylen niedriger Dichte, Polyethylen hoher Dichte, Polypropylen, Polyethylenglykol, Polyethylenoxid, Polyethylenterephthalat, Polyvinylalkohol, Polyvinylisobutylether, Polyvinylacetat und Polyvinylchlorid.

**[0102]** Besonders geeignete Copolymere können ausgewählt werden aus der Gruppe umfassend Copolymere aus Butylmethacrylat und Isobutylmethacrylat, Copolymere aus Methylvinylether und Maleinsäure mit erhöhtem Molekulargewicht, Copolymere aus Methylvinylether und Maleinsäuremonoethylester, Copolymere aus Methylvinylether und Maleinsäureanhydrid sowie Copolymere aus Vinylalkohol und Vinylacetat.

**[0103]** Weitere, zur Formulierung der Barrierschicht besonders geeignete Materialien sind Stärke gefülltes Polycaprolacton (WO98/20073), aliphatische Polyesteramide (DE 19 753 534 A1, DE 19 800 698 A1, EP 0 820 698 A1), aliphatische und aromatische Polyesterurethane (DE 19822979), Polyhydroxyalkanoate, insbesondere Polyhydroxybutyrate, Polyhydroxyvalerate), Casein (DE 4 309 528), Polylactide und Copolylactide (EP 0 980 894 A1). Die entsprechenden Beschreibungen werden hiermit als Referenz eingeführt und gelten als Teil der Offenbarung.

**[0104]** Ggf. können die vorstehend genannten Materialien mit weiteren üblichen, dem Fachmann bekannten Hilfsstoffen, vorzugsweise ausgewählt aus der Gruppe umfassend Weichmacher, Gleitmittel, Antioxidantien, wie z. B. Glycerinmonostearat, halbsynthetische Triglyceridderivate, halbsynthetische Glyceride, hydriertes Rizinusöl, Glycerinpalmistearat, Glycerinbehenat, Polyvinylpyrrolidon, Gelatine, Magnesiumstearat, Stearinsäure, Natriumstearat, Talkum, Natriumbenzoat, Borsäure und kolloidalem Silica, Fettsäuren, substituierte Triglyceride, Glyceride, Polyoxoalkylenglykole, Polyalkylenglykole und deren Derivate abgemischt werden.

**[0105]** Sofern die erfindungsgemäße Darreichungsform eine Trennschicht (Z') aufweist, kann diese, ebenso wie die nicht umhüllte Untereinheit (Y) vorzugsweise aus den vorstehend, für die Barrierschicht beschriebenen Materialien bestehen. Der Fachmann versteht, daß auch über die Dicke der Trennschicht die Freisetzung des Wirkstoffes bzw. der Komponente (c) und/oder (d) aus der jeweiligen Untereinheit gesteuert werden kann.

**[0106]** Die erfindungsgemäße Darreichungsform weist eine kontrollierte Freisetzung des Wirkstoffes auf. Sie eignet sich dabei vorzugsweise für eine 2x tägliche Verabreichung an Patienten.

**[0107]** Die erfindungsgemäße Darreichungsform kann einen oder mehrere Wirkstoffe mit Missbrauchspotential zumindest teilweise in einer darüber hinaus retardierten Form aufweisen, wobei die Retardierung mit Hilfe von üblichen, dem Fachmann bekannten Materialien und Verfahren erzielt werden kann, beispielsweise durch Einbetten des Wirkstoffes in eine retardierende Matrix oder durch das Aufbringen eines oder mehrerer retardierender Überzüge. Die Wirkstoffabgabe muss aber so gesteuert sein, daß die vorstehend genannten Bedingungen jeweils erfüllt sind, z.B. das bei bestimmungsgemäßer Applikation der Darreichungsform der Wirkstoff bzw. die Wirkstoffe praktisch komplett freigesetzt wird, bevor die ggf. vorhandenen Komponente (c) und/oder (d) eine beeinträchtigende Wirkung entfalten können. Außerdem darf durch die Zugabe von retardierenden Materialien keine Beeinträchtigung der notwendigen Härte erfolgen.

**[0108]** Die kontrollierte Freisetzung aus der erfindungsgemäßen Darreichungsform wird vorzugsweise durch Einbettung des Wirkstoffes in eine Matrix erzielt. Die als Matrixmaterialien dienenden Hilfsstoffe kontrollieren die Wirkstofffreisetzung. Matrixmaterialien können beispielsweise hydrophile, gelbildende Materialien sein, woraus die Wirkstofffreisetzung hauptsächlich durch Diffusion erfolgt, oder hydrophobe Materialien sein, woraus die Wirkstofffreisetzung hauptsächlich durch Diffusion aus den Poren in der Matrix erfolgt.

**[0109]** Als Matrixmaterialien können physiologisch verträgliche, hydrophile Materialien verwendet werden, welche dem Fachmann bekannt sind. Vorzugsweise werden als hydrophile Matrixmaterialien Polymere, besonders bevorzugt Celluloseether, Celluloseester und/oder Acrylharze verwendet. Ganz besonders bevorzugt werden als Matrixmaterialien Ethylcellulose, Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Hydroxymethylcellulose, Poly(meth)acrylsäure und/oder deren Derivate, wie deren Salze, Amide oder Ester eingesetzt.

**[0110]** Ebenfalls bevorzugt sind Matrixmaterialien aus hydrophoben Materialien, wie hydrophoben Polymeren, Wachsen, Fetten, langkettigen Fettsäuren, Fettalkoholen oder entsprechenden Estern oder Ethern oder deren Gemische. Besonders bevorzugt werden als hydrophobe Materialien Mono- oder Diglyceride von C12-C30-Fettsäuren und/oder C12-C30-Fettalkohole und/oder Wachse oder deren Gemische eingesetzt.

**[0111]** Es ist auch möglich, Mischungen der vorstehend genannten hydrophilen und hydrophoben Materialien als Matrixmaterialien einzusetzen.

**[0112]** Des weiteren können auch die Komponenten (C) und ggf. vorhandene Komponente (D), die zur Erzielung der erfindungsgemäß notwendigen Bruchfestigkeit von mindestens 500 N dienen, bereits als zusätzliche Matrixmaterialien dienen.

**[0113]** Sofern die erfindungsgemäße Darreichungsform zur oralen Applikation vorgesehen ist, kann sie bevorzugt auch einen magensaftresistenten Überzug aufweisen, der sich in Abhängigkeit vom pH-Wert der Freisetzungsumgebung auflöst. Durch diesen Überzug kann erreicht werden, daß die erfindungsgemäße Darreichungsform den Magen trakt unaufgelöst passiert und der Wirkstoff erst im Darm trakt zur Freisetzung gelangt. Vorzugsweise löst sich der magensaftresistente Überzug bei einem pH-Wert zwischen 5 und 7,5 auf.

**[0114]** Entsprechende Materialien und Verfahren zur Retardierung von Wirkstoffen sowie zum Aufbringen magensaftresistenter Überzüge sind dem Fachmann beispielsweise aus "Coated Pharmaceutical Dosage Forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" von Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1. Auflage, 1998, Medpharm Scientific Publishers bekannt. Die entsprechende Literaturbeschreibung wird hiermit als Referenz eingeführt und gilt als Teil der Offenbarung.

**Methode zur Bestimmung der Bruchfestigkeit**

[0115] Zur Überprüfung, ob ein Material als Komponente (C) oder (D) eingesetzt werden kann, wird das Material zu einer Tablette mit einem Durchmesser von 10 mm und einer Höhe von 5mm mit einer Kraft von 150 N, bei einer Temperatur entsprechend mindestens dem Erweichungspunkt des Materials und bestimmt mit Hilfe eines DSC-Diagramms des Materials verpresst. Mit so hergestellten Tabletten wird gemäß der Methode zur Bestimmung der Bruchfestigkeit von Tabletten, veröffentlicht im Europäischen Arzneibuch 1997, Seite 143, 144, Methode Nr. 2.9.8. unter Einsatz der nachstehend aufgeführten Apparatur die Bruchfestigkeit bestimmt. Als Apparatur für die Messung wird eine Zwick Materialprüfmaschine "Zwick Z 2.5", Materialprüfmaschine Fmax 2.5 kN mit einem Traversenweg von max. 1150 mm, der durch einen Aufbau mit Hilfe einer Säule und einer Spindel einzustellen ist, einen freien Arbeitsraum nach hinten von 100 mm und einer zwischen 0,1 bis 800 mm/min. einstellbaren Prüfgeschwindigkeit und einer Software: testControl eingesetzt. Es wird ein Druckstempel mit schraubbaren Einsätzen und einem Zylinder (Durchmesser 10 mm), ein Kraftaufnehmer, Fmax. 1 kN, Durchmesser 8 mm, Klasse 0.5 ab 10 N, Klasse 1 ab 2 N nach ISO 7500-1, mit Hersteller-Prüfzertifikat M nach DIN 55350-18 (Zwick-Bruttokraft Fmax 1,45 kN) zur Messung eingesetzt (alles Apparaturen der Firma Zwick GmbH & Co. KG, Ulm, Deutschland) mit der Bestell-Nr. BTC-FR 2.5 TH. D09 für die Prüfmaschine, der Bestell-Nr. BTC-LC 0050N. P01 für den Kraftaufnehmer, der Bestell-Nr. BO 70000 S06 für die Zentriervorrichtung. [0116] Figur 1 zeigt die Messung der Bruchfestigkeit einer Tablette, insbesondere die dafür eingesetzte Justierungsvorrichtung (6) der Tablette (4) vor und während der Messung. Darzu wird die Tablette (4) zwischen der oberen Druckplatte (1) und der unteren Druckplatte (3) der nicht dargestellten Vorrichtung zur Kraftaufbringung mit Hilfe von zwei 2-teiligen Einspannvorrichtungen, die jeweils mit der oberen bzw. unteren Druckplatte nach Einstellung des zur Aufnahme und zur Zentrierung der zu messenden Tablette notwendigen Abstands (5) fest verbunden (nicht dargestellt) werden. Zur Einstellung des Abstands (5) können die 2-teiligen Einspannvorrichtungen jeweils auf der Druckplatte, auf der sie gelagert sind, horizontal nach außen oder innen bewegt werden.

[0117] Als bruchfest bei einer bestimmten Krafteinwirkung werden auch die Tabletten eingestuft, bei denen kein Bruch feststellbar, aber ggf. eine plastische Verformung der Tablette durch die Krafteinwirkung erfolgt ist.

[0118] Bei den erfindungsgemäß erhaltenen Darreichungsformen wird die Bruchfestigkeit nach der aufgeführten Meßmethode bestimmt, wobei von Tabletten abweichenden Darreichungsformen ebenso geprüft werden.

[0119] Im Folgenden wird die Erfindung anhand von Beispielen erläutert. Diese Erläuterungen sind lediglich beispielhaft und schränken den allgemeinen Erfindungsgedanken nicht ein.

**Beispiele:**

[0120] In einer Reihe von Beispielen wurde Tramadolhydrochlorid als Wirkstoff verwendet. Tramadolhydrochlorid wurde, obwohl Tramadol kein Wirkstoff mit üblichem Mißbrauchspotential ist, da es nicht unter das Betäubungsmittelgesetz fällt, aber wodurch das experimenteller Arbeiten erleichtert wird. Tramadol ist außerdem ein Vertreter der Klasse der Opiode mit ausgezeichneter Wasserlöslichkeit.

**Beispiel 1****[0121]**

| Komponenten                                                      | Pro Tablette | Gesamtansatz |
|------------------------------------------------------------------|--------------|--------------|
| Tramadolhydrochlorid                                             | 100 mg       | 100 g        |
| Polyethylenoxid, NF, MG 7 000 000 (Polyox WSR303, Dow Chemicals) | 200 mg       | 200 g        |
| Gesamtgewicht                                                    | 300 mg       | 300 g        |

[0122] Tramadolhydrochlorid und Polyethylenoxidpulver wurden in einem Freifallmischer gemischt. Ein Tablettierwerkzeug mit Oberstempel, Unterstempel und Matrice für Tabletten mit 10 mm Durchmesser und einem Wölbungsradius von 8 mm wurde in einem Heizschrank auf 80°C erhitzt. Mittels des erhitzten Werkzeugs wurden jeweils 300 mg der Pulvermischung verpreßt, wobei der Preßdruck für mindestens 15 s aufrechterhalten wurde durch Einspannen des Tablettierwerkzeugs in einen Schraubstock.

[0123] Die Bruchfestigkeit der Tabletten wurde gemäß der angegebenen Methode mit der angegebenen Apparatur bestimmt. Bei einer Krafteinwirkung von 500 N trat kein Bruch der Tabletten auf.

[0124] Die Tablette konnte mit einem Hammer nicht zerkleinert werden. Dies war auch mit Hilfe von Mörser und Pistill nicht möglich.

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[0125] Die in-vitro-Freisetzung des Wirkstoffs aus der Zubereitung wurde in der Blattrührerapparatur nach Pharm. Eur. bestimmt. Die Temperatur des Freisetzungsmediums betrug 37°C und die Umdrehungsgeschwindigkeit des Rührers 75 min<sup>-1</sup>. Zu Beginn der Untersuchung wurde jede Tablette in jeweils 600 ml künstlichen Magensaft pH 1,2 gegeben. Nach 30 Minuten wurde durch Zugabe von Lauge der pH-Wert auf 2,3 erhöht, nach weiteren 90 Minuten auf pH 6,5 und nach nochmals 60 weiteren Minuten auf pH 7,2. Die jeweils zu einem Zeitpunkt im Lösungsmedium befindliche freigesetzte Menge des Wirkstoffs wurde spektralphotometrisch bestimmt.

| Zeit    | Freigesetzte Menge |
|---------|--------------------|
| 30 min  | 15 %               |
| 240 min | 52 %               |
| 480 min | 80 %               |
| 720 min | 99 %               |

### Beispiel 2

[0126] Die Pulvermischung aus Beispiel 1 wurde in Portionen zu 300 mg auf 80°C erhitzt und in die Matrize des Tablettierwerkzeugs eingefüllt. Anschließend erfolgte die Verpressung. Die Tablette weist dieselben Eigenschaften auf wie die Tablette nach Beispiel 1 hergestellt.

### Beispiel 3

[0127]

| Rohstoff                                                          | Pro Tablette | Gesamtansatz |
|-------------------------------------------------------------------|--------------|--------------|
| Tramadolhydrochlorid                                              | 50 mg        | 100 g        |
| Polyethylenoxid, NF, MG 7 000 000 (Polyox WSR 303, Dow Chemicals) | 100 mg       | 200 g        |
| Gesamtgewicht                                                     | 150 mg       | 300 g        |

[0128] Tramadolhydrochlorid und die vorstehend angegebenen Komponenten wurden in einem Freifallmischer gemischt. Ein Tablettierwerkzeug mit Oberstempel, Unterstempel und Matrize für Tabletten mit 7 mm Durchmesser wurde in einem Heizschrank auf 80°C erhitzt. Mittels des erhitzten Werkzeugs wurden jeweils 150 mg der Pulvermischung verpreßt, wobei der Preßdruck für mindestens 15 s durch Einspannen des Tablettierwerkzeugs in einen Schraubstock aufrechterhalten wurde.

[0129] Die Bruchfestigkeit der Tabletten wurde gemäß der angegebenen Methode mit Hilfe der angegebenen Apparatur bestimmt. Bei einer Krafteinwirkung von 500 N trat kein Bruch der Tabletten auf.

[0130] Die in-vitro-Freisetzung des Wirkstoffs wurde wie in Beispiel 1 bestimmt und betrug:

| Zeit    | Freigesetzte Menge |
|---------|--------------------|
| 30 min  | 15 %               |
| 240 min | 62 %               |
| 480 min | 88 %               |
| 720 min | 99 %               |

### Beispiel 4

[0131]

| Rohstoff             | Pro Tablette | Gesamtansatz |
|----------------------|--------------|--------------|
| Tramadolhydrochlorid | 100 mg       | 100 g        |

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| Rohstoff                                                          | Pro Tablette | Gesamtansatz |
|-------------------------------------------------------------------|--------------|--------------|
| Polyethylenoxid, NF, MG 7 000 000 (Polyox WSR 303, Dow Chemicals) | 180 mg       | 180 g        |
| Xanthan, NF                                                       | 20 mg        | 20 g         |
| Gesamtgewicht                                                     | 300 mg       | 300 g        |

[0132] Tramadolhydrochlorid, Xanthan und Polyethylenoxid wurden in einem Freifallmischer gemischt. Ein Tablettierwerkzeug mit Oberstempel, Unterstempel und Matrize für Tabletten mit 10 mm Durchmesser und einem Wölbungsradius von 8 mm wurde in einem Heizschrank auf 80°C erhitzt. Mittels des erhitzten Werkzeugs wurden jeweils 300 mg der Pulvermischung verpreßt, wobei der Preßdruck für mindestens 15 s durch Einspannen des Tablettierwerkzeugs in einen Schraubstock aufrechterhalten wurde.

[0133] Die Bruchfestigkeit der Tabletten wurde gemäß der angegebenen Methode mit Hilfe der angegebenen Apparatur gemessen. Bei einer Krafteinwirkung von 500 N trat kein Bruch der Tabletten auf. Die Tabletten wurden etwas plastisch verformt.

[0134] Die in-vitro-Freisetzung des Wirkstoffs aus der Zubereitung wurde wie in Beispiel 1 bestimmt und betrug:

| Zeit    | Freigesetzte Menge |
|---------|--------------------|
| 30 min  | 14 %               |
| 240 min | 54 %               |
| 480 min | 81 %               |
| 720 min | 99 %               |

[0135] Die Tabletten konnten mit einem Messer in Stücke mit bis zu ca. 2 mm Kantenlänge zerschnitten werden. Eine weitere Zerkleinerung bis zur Pulverisierung war nicht möglich. Beim Versetzen der Stücke mit Wasser bildet sich ein hochviskoses Gel. Das Gel war nur sehr schwer durch eine Injektionskanüle von 0,9 mm zu pressen. Beim Einspritzen des Gels in Wasser mischte sich das Gel nicht spontan mit Wasser, sondern blieb visuell unterscheidbar.

## Beispiel 5

[0136]

| Rohstoff                                                          | Pro Tablette | Gesamtansatz |
|-------------------------------------------------------------------|--------------|--------------|
| Tramadolhydrochlorid                                              | 50 mg        | 100 g        |
| Polyethylenoxid, NF, MG 7 000 000 (Polyox WSR 303, Dow Chemicals) | 90 mg        | 180 g        |
| Xanthan, NF                                                       | 10 mg        | 20 g         |
| Gesamtgewicht                                                     | 300 mg       | 300 g        |

[0137] Tramadolhydrochlorid, Xanthan und Polyethylenoxid wurden in einem Freifallmischer gemischt. Ein Tablettierwerkzeug mit Oberstempel, Unterstempel und Matrize für Oblongtabletten mit 10 mm Länge und 5 mm Breite wurde in einem Heizschrank auf 90°C erhitzt. Mittels des erhitzten Werkzeugs wurden jeweils 150 mg der Pulvermischung verpreßt, wobei der Preßdruck für mindestens 15 s durch Einspannen des Tablettierwerkzeugs in einen Schraubstock aufrechterhalten.

[0138] Die Bruchfestigkeit der Tabletten wurde gemäß der angegebenen Methode mit Hilfe der angegebenen Apparatur gemessen. Bei einer Krafteinwirkung von 500 N trat kein Bruch der Tabletten auf. Die Tabletten wurden etwas plastisch verformt.

[0139] Die in-vitro-Freisetzung des Wirkstoffs aus der Zubereitung wurde wie in Beispiel 1 bestimmt und betrug:

| Zeit   | Freigesetzte Menge |
|--------|--------------------|
| 30 min | 22 %               |



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| Zeit    | Freigesetzte Menge |
|---------|--------------------|
| 120 min | 50 %               |
| 240 min | 80 %               |
| 360 min | 90 %               |
| 480 min | 99 %               |

[0140] Die Tabletten konnten zu Stückchen bis zu ca. 2 mm Kantenlänge zerschnitten, aber nicht pulverisiert werden. Bei Versetzen der Stücke mit Wasser bildet sich ein hochviskoses Gel. Das Gel war nur sehr schwer durch eine Injektionskanüle von 0,9 mm zu pressen. Bei Einspritzen des Gels in Wasser mischte sich das Gel nicht spontan mit Wasser, sondern blieb visuell unterscheidbar.

### Beispiel 6

[0141] Wie in Beispiel 1 beschrieben, wurde eine Tablette mit folgender Zusammensetzung hergestellt:

| Komponenten                                                      | ProTablette | Pro Ansatz |
|------------------------------------------------------------------|-------------|------------|
| Oxycodon Hydrochlorid                                            | 20,0 mg     | 0,240 g    |
| Xanthan NF                                                       | 20,0 mg     | 0,240 g    |
| Polyethylenoxid, NF, MG 7 000 000 (Polyox WSR 303 Dow Chemicals) | 110,0 mg    | 1,320 g    |
| Gesamtgewicht                                                    | 150,0 mg    | 1,800 g    |

[0142] Die Freisetzung des Wirkstoffs wurde wie folgt bestimmt:

[0143] Die in-vitro-Freisetzung des Wirkstoffs aus der Tablette wurde in der Blattrührerapparatur nach Pharm. Eur. bestimmt. Die Temperatur des Freisetzungsmediums betrug 37°C und die Umdrehungsgeschwindigkeit 75 U pro Minute. Als Freisetzungsmedium diente der in der USP beschriebene Phosphatpuffer pH 6,8. Die zum jeweiligen Prüfzeitpunkt im Lösungsmittel befindliche Menge des Wirkstoffs wurde spektralphotometrisch bestimmt.

| Zeit    | Mittelwert |
|---------|------------|
| 0 min   | 0 %        |
| 30 min  | 17 %       |
| 240 min | 61 %       |
| 480 min | 90 %       |
| 720 min | 101,1 %    |

[0144] Die Bruchfestigkeit der Tabletten wurde gemäß der angegebenen Methode mit Hilfe der angegebenen Apparatur gemessen. Bei einer Krafterwirkung von 500 N trat kein Bruch der Tabletten auf.

[0145] Die Tabletten konnten zu Stückchen bis zu ca. 2 mm Kantenlänge zerschnitten, aber nicht pulverisiert werden. Bei Versetzen der Stücke mit Wasser bildet sich ein hochviskoses Gel. Das Gel war nur sehr schwer durch eine Injektionskanüle von 0,9 mm zu pressen. Bei Einspritzen des Gels in Wasser mischte sich das Gel nicht spontan mit Wasser, sondern blieb visuell unterscheidbar.

### Beispiel 7:

[0146]

| Komponenten  | Pro Tablette | Gesamtansatz |
|--------------|--------------|--------------|
| Tramadol HCL | 100,0 mg     | 2,0 g        |

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(fortgesetzt)

| Komponenten                                                            | Pro Tablette | Gesamtansatz |
|------------------------------------------------------------------------|--------------|--------------|
| Polyethylenoxid, NF, MG 7 000 000 (Polyox WSR 303, Dow Chemicals)      | 221,0 mg     | 4,42 g       |
| Hydroxypropylmethylcellulose (Metholose 90 SH 100 000 cP von ShinEtsu) | 20,0 mg      | 0,4 g        |
| Butylhydroxytoluol (BHT)                                               | 0,2 mg       | 0,004 g      |
| Gesamtgewicht                                                          | 341,2 mg     | 6,824 g      |

[0147] Die angegebene BHT-Menge wurde in Ethanol (96%) gelöst, so dass man eine 7,7%-ige (m/m) ethanolische Lösung erhielt. Diese wurde mit dem Polyethylenoxid gemischt und anschließend bei 40°C für 12 h getrocknet. Alle weiteren Komponenten wurden dieser getrockneten Mischung zugesetzt und in einem Freifallmischer für 15 min gemischt.

[0148] Die Herstellung der Tabletten erfolgte nach demselben Verfahren, wie es in Beispiel 1 angegeben. Es wurden runde Stempel (Durchmesser 10 mm) mit einem Wölbungsradius von 8 mm verwendet.

[0149] Die Bruchfestigkeit der Tabletten wurde nach der vorstehend beschriebenen Methode bestimmt. Bei einer Krafteinwirkung von 500 N trat kein Bruch auf. Die Tablette konnte weder mit einem Hammer noch mit Hilfe von Mörser und Pistill zerkleinert werden.

[0150] Die in vitro Freisetzung des Wirkstoffs aus der Darreichungsform wurde gemäß den Angaben in Beispiel 1 zur Bestimmung der Freisetzung durchgeführt.

| Zeit    | Freigesetzte Wirkstoffmenge |
|---------|-----------------------------|
| 30 min  | 17 %                        |
| 240 min | 59 %                        |
| 480 min | 86 %                        |
| 720 min | 98 %                        |

## [0151] Beispiel 8

| Komponenten                                                            | Pro Tablette | Gesamtansatz |
|------------------------------------------------------------------------|--------------|--------------|
| Tramadol HCL                                                           | 100,0 mg     | 2,0 g        |
| Polyethylenoxid, NF, MG 7 000 000 (Polyox WSR 303, Dow Chemicals)      | 221,0        | 4,42 g       |
| Hydroxypropylmethylcellulose (Metholose 90 SH 100 000 cP von ShinEtsu) | 20,0 mg      | 0,4 g        |
| Gesamtgewicht                                                          | 341,0 mg     | 6,82 g       |

[0152] Die einzelnen Komponenten wurden in einem Freifallmischer für 15 Minuten gemischt. Die Herstellung der Tabletten erfolgte gemäß Beispiel 1 mit einem heißen Tablettierwerkzeug. Es wurden runde Stempel (Durchmesser 10 mm) mit einem Wölbungsradius von 8 mm verwendet.

[0153] Die Bruchfestigkeit der Tabletten wurde nach der angegebenen Methode bestimmt. Bei einer Krafteinwirkung von 500 N trat kein Bruch auf. Die Tablette konnte weder mit einem Hammer noch mit Hilfe von Mörser und Pistill zerkleinert werden.

[0154] Die in vitro Freisetzung des Wirkstoffs aus der Zubereitung wurde wie in Beispiel 1 angegeben bestimmt.

| Zeit    | Freigesetzte Wirkstoffmenge |
|---------|-----------------------------|
| 30 min  | 16 %                        |
| 240 min | 57 %                        |
| 480 min | 84 %                        |
| 720 min | 96%                         |

Patentansprüche

1. Gegen Missbrauch gesicherte, ohne Extrusion thermogeformte Darreichungsform, **dadurch gekennzeichnet, dass** sie neben einem oder mehreren Wirkstoffen mit Mißbrauchspotential (A) sowie ggf. physiologisch verträglichen Hilfsstoffen (B) mindestens ein synthetisches oder natürliches Polymer (C) und ggf. mindestes ein Wachs (D) aufweist, wobei die Komponente (C) und die gegebenenfalls vorhandene Komponente (D) eine Bruchfestigkeit von mindestens 500 N aufweist.
2. Darreichungsform gemäß Anspruch 1, **dadurch gekennzeichnet, dass** sie in Form einer Tablette vorliegt.
3. Darreichungsform gemäß Anspruch 1, **dadurch gekennzeichnet, dass** sie in multipartikulärer Form, vorzugsweise in Form von Mikrotabletten, Mikropellets, Granulaten, Sphäroiden, Perlen oder Pellets, ggf. zu Tabletten verpreßt oder in Kapseln abgefüllt, vorliegt.
4. Darreichungsform gemäß einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, dass** sie als Polymer (C) wenigstens ein Polymer ausgewählt aus der Gruppe umfassend Polyethylenoxid, Polymethylenoxid, Polypropylenoxid, Polyethylen, Polypropylen, Polyvinylchlorid, Polycarbonat, Polystyrol, Polyacrylat, Copolymerisate und deren Mischungen, vorzugsweise Polyethylenoxid, enthält.
5. Darreichungsform gemäß einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet, dass** das Polyethylenoxid (C) ein Molekulargewicht von mindestens 0,5 Mio. aufweist.
6. Darreichungsform gemäß Anspruch 5, **dadurch gekennzeichnet, dass** das Molekulargewicht des Polyethylenoxids (C) mindestens 1 Mio. beträgt.
7. Darreichungsform gemäß Anspruch 6, **dadurch gekennzeichnet, dass** das Molekulargewicht des Polyethylenoxids (C) 1-15 Mio. beträgt.
8. Darreichungsform gemäß einem der Ansprüche 1 bis 7, **dadurch gekennzeichnet, dass** sie als Wachs (D) wenigstens ein natürliches, halbsynthetisches oder synthetisches Wachs mit einem Erweichungspunkt von wenigstens 60°C enthält.
9. Darreichungsform gemäß Anspruch 8, **dadurch gekennzeichnet, dass** das Wachs (D) Camaubawachs oder Bienenwachs ist.
10. Darreichungsform gemäß einem der Ansprüche 1 bis 9, **dadurch gekennzeichnet, dass** die Komponente(n) (C) und gegebenenfalls (D) in solchen Mengen vorliegt, dass die Darreichungsform eine Bruchfestigkeit von mindestens 500 N aufweist.
11. Darreichungsform gemäß einem der Ansprüche 1 bis 10, **dadurch gekennzeichnet, dass** der Wirkstoff (A) wenigstens ein Wirkstoff ausgewählt aus der Gruppe umfassend Opiode, Tranquillantien, Stimulatione, Barbiturate und weitere Betäubungsmittel ist.
12. Darreichungsform gemäß einem der Ansprüche 1 bis 11, **dadurch gekennzeichnet, dass** sie noch mindestens eine der nachfolgenden Komponenten a)-f) aufweist:
  - (a) wenigstens einen den Nasen- und/oder Rachenraum reizenden Stoff,
  - (b) wenigstens ein viskositäts erhöhendes Mittel, das in einem mit Hilfe einer notwendigen Mindestmenge an einer wäßrigen Flüssigkeit aus der Darreichungsform gewonnenen Extrakte ein Gel bildet, welches vorzugsweise beim Einbringen in eine weitere Menge einer wäßrigen Flüssigkeit visuell unterscheidbar bleibt,
  - (c) wenigstens einen Antagonisten für den Wirkstoff bzw. die Wirkstoffe mit Missbrauchspotential
  - (d) wenigstens ein Emetikum.
  - (e) wenigstens einen Farbstoff als aversives Mittel
  - (f) wenigstens einen Bitterstoff.
13. Darreichungsform gemäß Anspruch 12, **dadurch gekennzeichnet, dass** der Reizstoff gemäß Komponente (a) ein Brennen, einen Juckreiz, einen Niesreiz, eine vermehrte Sekretbildung oder eine Kombination mindestens zweier dieser Reize verursacht.

14. Darreichungsform gemäß Anspruch 12 oder 13, **dadurch gekennzeichnet, dass** der Reizstoff gemäß Komponente (a) auf einem oder mehreren Inhaltsstoffen wenigstens einer Scharfstoffdroge basiert.

15. Darreichungsform gemäß Anspruch 14, **dadurch gekennzeichnet, dass** die Scharfstoffdroge wenigstens eine Droge ausgewählt aus der Gruppe umfassend *Allii sativi* Bulbus, *Asari* Rhizoma c. *Herba*, *Calami* Rhizoma, *Capsici* Fructus (Paprika), *Capsici* Fructus acer (Cayennepfeffer), *Curcumae* longae Rhizoma, *Curcumae* xanthorrhizae Rhizoma, *Galangae* Rhizoma, *Myristicae* Semen, *Piperis* nigri Fructus (Pfeffer), *Sinapis* albae (Erucae) Semen, *Sinapis* nigri Semen, *Zedoariae* Rhizoma und *Zingiberis* Rhizoma, besonders bevorzugt wenigstens eine Droge ausgewählt aus der Gruppe umfassend *Capsici* Fructus (Paprika), *Capsici* Fructus acer (Cayennepfeffer) und *Piperis* nigri Fructus (Pfeffer) ist.

16. Darreichungsform gemäß Anspruch 14 oder 15, **dadurch gekennzeichnet, dass** der Inhaltsstoff der Scharfstoffdroge als eine o-Methoxy(Methyl)-phenol-Verbindung, eine Säureamid-Verbindung vorliegt, ein Senföl oder eine Sulfidverbindung ist oder sich von einer solchen Verbindung ableitet.

17. Darreichungsform gemäß einem der Ansprüche 14 bis 16, **dadurch gekennzeichnet, dass** der Inhaltsstoff der Scharfstoffdroge wenigstens ein Inhaltsstoff ausgewählt aus der Gruppe umfassend Myristicin, Elemicin, Isoeugenol,  $\beta$ -Asaron, Safrol, Gingerolen, Xanthorrhizol, Capsaicinoiden, vorzugsweise Capsaicin, Piperin, vorzugsweise trans-Piperin, Glucosinolate, vorzugsweise auf Basis von nichtflüchtigen Senfölen, besonders bevorzugt auf Basis von p-Hydroxybenzylsenföl, Methylmercaptosenföl oder Methylsulfonylsenföl, und eine von diesen Inhaltsstoffen abgeleiteten Verbindung ist.

18. Darreichungsform gemäß einem der Ansprüche 12 bis 17, **dadurch gekennzeichnet, dass** die Komponente (b) wenigstens ein viskositätserhöhendes Mittel ausgewählt aus der Gruppe umfassend mikrokristalline Cellulose mit 11 Gew.-% Carboxymethylcellulose-Natrium (Avicel® RC 591), Carboxymethylcellulose-Natrium (Blanose®, CMC-Na C300P®, Frimulsion BLC-5®, Tylose C300 P®), Polyacrylsäure (Carbopol® 980 NF, Carbopol® 981), Johannisbrotkernmehl (Cesagum® LA-200, Cesagum® LID/150, Cesagum® LN-1), Pektine aus Citrusfrüchten oder Äpfeln (Cesapectin® HM Medium Rapid Set), Wachsmaisstärke (C\*Gel 04201®), Natriumalginat (Frimulsion ALG (E401)®), Guarkernmehl (Frimulsion BM®, Polygum 26/1-75®), Iota-Carrageen (Frimulsion D021®), Karaya Gummi, Gellangummi (Kelcogel F®, Kelcogel LT100®), Galaktomannan (Meyprogat 150®), Tarakernmehl (Polygum 43/1®), Propylenglykoalginat (Protanal-Ester SD-LB®), Apfelpektin, Natrium-Hyaluronat, Tragant, Taragummi (Vidogum SP 200®), fermentiertes Polysaccharid- Welan Gum (K1A96) und Xanthan-Gummi (Xantural 180®) ist.

19. Darreichungsform gemäß einem der Ansprüche 12 bis 18, **dadurch gekennzeichnet, dass** die Komponente (c) wenigstens ein Opioid-Antagonist ausgewählt aus der Gruppe umfassend Naloxon, Naltrexon, Nalmefen, Nalid, Nalmexon, Nalorphin, Naluphin und eine entsprechende physiologisch verträgliche Verbindung, insbesondere eine Base, ein Salz oder Solvat ist.

20. Darreichungsform gemäß einem der Ansprüche 12 bis 18, **dadurch gekennzeichnet, dass** als Komponente (c) wenigstens ein Neuroleptikum als Stimulanz-Antagonist, vorzugsweise ausgewählt aus der Gruppe umfassend Haloperidol, Promethacin, Fluophenozin, Perphenazin, Levomepromazin, Thioridazin, Perazin, Chlorpromazin, Chlorprothexin, Zucklopantexol, Flupentexol, Prithipendyl, Zotepin, Penperidol, Pipameron, Melperol und Bromperidol ist.

21. Darreichungsform gemäß einem der Ansprüche 12 bis 20, **dadurch gekennzeichnet, dass** das Emetikum gemäß Komponente (d) auf einem oder mehreren Inhaltsstoffen von *Radix Ipecacuanhae* (Brechwurzel), vorzugsweise auf dem Inhaltsstoff Emetin basiert, und/oder Apomorphin ist.

22. Darreichungsform gemäß einem der Ansprüche 12 bis 21, **dadurch gekennzeichnet, dass** die Komponente (e) wenigstens ein physiologisch verträglicher Farbstoff ist.

23. Darreichungsform gemäß einem der Ansprüche 12 bis 22, **dadurch gekennzeichnet, dass** die Komponente (f) wenigstens ein Bitterstoff ausgewählt aus der Gruppe umfassend Aromaöle, vorzugsweise Pfefferminzöl, Eukalyptusöl, Bittermandelöl, Menthol und deren Mischungen, Fruchtaromastoffe, vorzugsweise von Zitronen, Orangen, Limonen, Grapefruit und deren Mischungen aus wenigstens 2 Komponenten, Denatoniumbenzoat und deren Mischungen aus wenigstens 2 Komponenten ist.

24. Darreichungsform gemäß einem der Ansprüche 12 bis 23, **dadurch gekennzeichnet, dass** der Wirkstoff bzw. die

Wirkstoffe (A) von der Komponente (c) und/oder (d) und/oder (f) räumlich getrennt, vorzugsweise ohne direkten Kontakt sind, wobei der Wirkstoff bzw. die Wirkstoffe (A) bevorzugt in wenigstens einer Untereinheit (X) und die Komponenten (c) und/oder (d) und/oder (f) in wenigstens einer Untereinheit (Y) vorliegen und die Komponenten (c) und/oder (d) und/oder (f) aus der Untereinheit (Y) bei bestimmungsgemäßer Applikation der Darreichungsform im Körper bzw. bei Einnahme nicht ihre Wirkung entfalten.

25. Darreichungsform gemäß einem der Ansprüche 1 bis 24, **dadurch gekennzeichnet, dass** sie wenigstens einen Wirkstoff zumindest teilweise in retardierter Form enthält.

26. Darreichungsform gemäß Anspruch 25, **dadurch gekennzeichnet, dass** jeder der Wirkstoffe mit Missbrauchspotential (A) in einer Retardmatrix vorliegt.

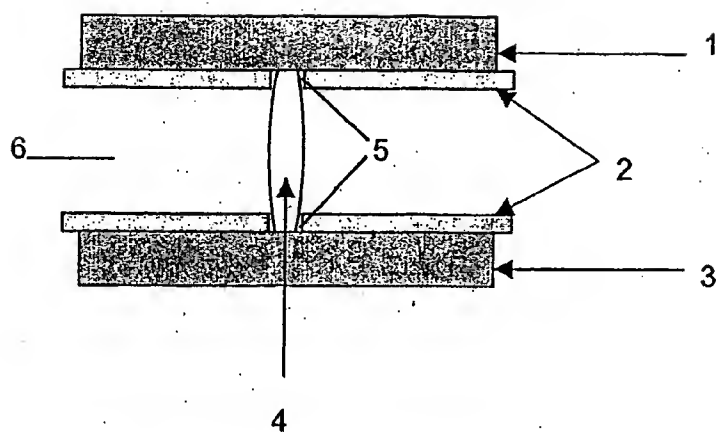
27. Darreichungsform gemäß Anspruch 26, **dadurch gekennzeichnet, dass** die Komponente (C) und/oder die gegebenenfalls vorhandene Komponente (D) auch als Retardmatrixmaterial dient.

28. Verfahren zur Herstellung einer Darreichungsform gemäß einem der Ansprüche 1 bis 27, **dadurch gekennzeichnet, dass** man ohne Einsatz eines Extruders

die Komponenten (A), (B), (C) und die gegebenenfalls vorhandene Komponente (D) mischt sowie die ggf. vorhandenen Komponenten (a) bis (f) mitmischt oder, soweit notwendig, separat unter Zusatz der Komponente (C) und gegebenenfalls (D) mischt und die resultierende Mischung oder die resultierenden Mischungen ggf. nach einer Granulierung zu der Darreichungsform unter vorangehender oder gleichzeitiger Wärmeeinwirkung durch Krafteinwirkung formt.

29. Verfahren gemäß Anspruch 28, **dadurch gekennzeichnet, dass** die Granulierung gemäß einer Schmelz- oder Feuchtgranulierung durchgeführt wird.

30. Darreichungsform nach einem der Ansprüche 1 bis 27 erhältlich nach Verfahren gemäß Anspruch 28 oder 29.



Figur 1



Europäisches  
Patentamt

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Nummer der Anmeldung  
EP 06 02 4704

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EPO FORM/ 1503 29 82 (P04C03)

**ANHANG ZUM EUROPÄISCHEN RECHERCHENBERICHT  
 ÜBER DIE EUROPÄISCHE PATENTANMELDUNG NR.**

EP 06 02 4704

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten europäischen Recherchenbericht angeführten Patentedokumente angegeben.

Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am  
 Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr

18-10-2007

| Im Recherchenbericht<br>angeführtes Patentedokument |    | Datum der<br>Veröffentlichung |       | Mitglied(er) der<br>Patentfamilie |  | Datum der<br>Veröffentlichung |
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Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/02



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*Diese Liste der vom Anmelder aufgeführten Dokumente wurde ausschließlich zur Information des Lesers aufgenommen und ist nicht Bestandteil des europäischen Patentdokumentes. Sie wurde mit größter Sorgfalt zusammengestellt; das EPA übernimmt jedoch keinerlei Haftung für etwaige Fehler oder Auslassungen.*

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US 20030068392A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0068392 A1**  
**Sackler** (43) **Pub. Date: Apr. 10, 2003**

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(54) **PHARMACEUTICAL FORMULATION  
CONTAINING OPIOID AGONIST, OPIOID  
ANTAGONIST AND IRRITANT**

**Publication Classification**

(51) **Int. Cl.<sup>7</sup>** ..... **A61K 35/78**; A61K 31/165;  
A61K 31/485

(76) **Inventor: Richard Sackler, Greenwich, CT (US)**

(52) **U.S. Cl.** ..... **424/760**; 514/2; 514/282;  
514/622

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(57) **ABSTRACT**

(21) **Appl. No.: 10/214,409**

(22) **Filed: Aug. 6, 2002**

**Related U.S. Application Data**

(60) **Provisional application No. 60/310,515, filed on Aug.  
6, 2001.**

Disclosed in certain embodiments is an oral dosage form comprising: a therapeutically effective amount of an opioid analgesic; an opioid antagonist; and an irritant in an effective amount to impart an irritating sensation to an abuser upon administration of the dosage form after tampering.

**PHARMACEUTICAL FORMULATION  
CONTAINING OPIOID AGONIST, OPIOID  
ANTAGONIST AND IRRITANT**

[0001] This application claims the benefit of U.S. Provisional Serial No. 60/310,515, filed Aug. 6, 2001, hereby incorporated by reference in its entirety.

**BACKGROUND OF THE INVENTION**

[0002] Opioid analgesics are sometimes the subject of abuse. Typically, a particular dose of an opioid analgesic is more potent when administered parenterally as compared to the same dose administered orally. Therefore, one popular mode of abuse of oral opioid formulations involves the extraction of the opioid from the dosage form, and the subsequent injection of the opioid (using any "suitable" vehicle for injection) in order to achieve a "high."

[0003] In the prior art, there have previously been attempts to control the abuse potential associated with opioid analgesics. For example, the combination of immediate release pentazocine and naloxone has been utilized in tablets available in the United States, commercially available as Talwin®Nx from Sanofi-Winthrop. Talwin®Nx is indicated for the relief of moderate to severe pain. Talwin®Nx contains immediate release pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. The amount of naloxone present in this combination has low activity when taken orally, and minimally interferes with the pharmacologic action of pentazocine. However, this amount of naloxone given parenterally has profound antagonistic action to narcotic analgesics. Thus, the inclusion of naloxone is intended to curb a form of misuse of oral pentazocine which occurs when the dosage form is solubilized and injected. Therefore, this dosage has lower potential for parenteral misuse than previous oral pentazocine formulations.

[0004] A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of severe pain since 1978 (Valoron®N, Goedecke). The rationale for the combination of these drugs is effective pain relief and the prevention of tilidine addiction through naloxone-induced antagonisms at the morphine receptor. A fixed combination of buprenorphine and naloxone was introduced in 1991 in New Zealand (Temgesic®Nx, Reckitt & Colman) for the treatment of pain.

[0005] Purdue Pharma L.P. currently markets sustained-release oxycodone in dosage forms containing 10, 20, 40, and 80 mg oxycodone hydrochloride under the tradename OxyContin.

[0006] U.S. Pat. Nos. 5,266,331; 5,508,042; 5,549,912 and 5,656,295 disclose sustained release oxycodone formulations.

[0007] U.S. Pat. Nos. 4,769,372 and 4,785,000 to Kreek describe methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility by administering 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of an opioid antagonist having little to no systemic antagonist activity when administered orally, from 1 to 5 times daily.

[0008] U.S. Pat. No. 6,228,863 to Palermo et al. describes compositions and methods of preventing abuse of opioid dosage forms.

[0009] WO 99/32119 to Kaiko et al. describes compositions and methods of preventing abuse of opioid dosage forms.

[0010] U.S. Pat. No. 5,472,943 to Crain et al. describes methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist.

[0011] Additionally, Shaw et al., U.S. Pat. No. 3,980,766, relates to drugs which are suitable for therapy in the treatment of narcotic drug addiction by oral use, e.g., methadone, formulated to prevent injection abuse through concentration of the active component in aqueous solution by incorporating in a solid dosage or tablet form of such drug an ingestible solid having thickening properties which cause rapid increase in viscosity upon concentration of an aqueous solution thereof.

[0012] However, there still exists a need for a safe and effective treatment of pain with opioid analgesic dosage forms which are less subject to abuse than current therapies.

[0013] All documents cited herein, including the foregoing, are incorporated by reference in their entireties for all purposes.

**OBJECTS AND SUMMARY OF THE  
INVENTION**

[0014] It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less parenteral abuse than other dosage forms.

[0015] It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less intranasal abuse than other dosage forms.

[0016] It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less oral abuse than other dosage forms.

[0017] It is a further object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less diversion than other dosage forms.

[0018] It is a further object of certain embodiments of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the abuse potential of the dosage form.

[0019] It is a further object of certain embodiments of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less abuse potential.

[0020] These objects and others are achieved by the present invention, which is directed in part to an oral dosage form comprising an opioid analgesic; an opioid antagonist; and at least one aversive agent for reducing the abuse of the opioid analgesic.

[0021] In certain embodiments of the present invention, the oral dosage forms of the present invention comprising an opioid analgesic; an opioid antagonist; and an aversive agent or agents as a component(s) of the dosage form helps to

prevent injection abuse by decreasing the “attractiveness” of the dosage form to a potential abuser.

[0022] In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a bittering agent to discourage an abuser from tampering with the dosage form and thereafter inhaling or swallowing the tampered dosage form. Preferably, the bittering agent is released when the dosage form is tampered with and provides an unpleasant taste to the abuser upon inhalation and/or swallowing of the tampered dosage form.

[0023] In certain embodiments of the present invention, the dosage form comprises an aversive agent such as an irritant to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form. Preferably, the irritant is released when the dosage form is tampered with and provides a burning or irritating effect to the abuser upon inhalation, injection, and/or swallowing the tampered dosage form.

[0024] In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a gelling agent to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form. Preferably, the gelling agent is released when the dosage form is tampered with and provides a gel-like quality to the tampered dosage form which slows the absorption of the opioid analgesic such that an abuser is less likely to obtain a rapid “high”. In certain preferred embodiments, when the dosage form is tampered with and exposed to a small amount (e.g., less than about 10 ml) of an aqueous liquid (e.g., water), the dosage form will be unsuitable for injection and/or inhalation. Upon the addition of the aqueous liquid, the tampered dosage form preferably becomes thick and viscous, rendering it unsuitable for injection. The term “unsuitable for injection” is defined for purposes of the present invention to mean that one would have substantial difficulty injecting the dosage form (e.g., due to pain upon administration or difficulty pushing the dosage form through a syringe) due to the viscosity imparted on the dosage form, thereby reducing the potential for abuse of the opioid analgesic in the dosage form. In certain embodiments, the gelling agent is present in such an amount in the dosage form that attempts at evaporation (by the application of heat) to an aqueous mixture of the dosage form in an effort to produce a higher concentration of the therapeutic agent, produces a highly viscous substance unsuitable for injection.

[0025] When nasally inhaling the tampered dosage form, the gelling agent can become gel like upon administration to the nasal passages due to the moisture of the mucous membranes. This also makes such formulations aversive to nasal administration, as the gel will stick to the nasal passage and minimize absorption of the abusable substance.

[0026] In certain embodiments of the present invention, the dosage form comprises a combination of any or all of the aforementioned aversive agents (e.g., a bittering agent, an irritant, and/or a gelling agent) to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, and/or swallowing the tampered dosage form.

[0027] Embodiments specifically contemplated include bittering agent; gelling agent; irritant; bittering agent and gelling agent; bittering agent and irritant; gelling agent and

irritant; bittering agent and gelling agent; bittering agent and irritant; gelling agent and irritant; and bittering agent and gelling agent and irritant.

[0028] In certain preferred embodiments, the dosage forms are controlled release oral dosage forms comprising a therapeutically effective amount of an opioid analgesic and an opioid antagonist together with one or more of the aversive agents described above such that the dosage form provides effective pain relief for at least about 12 hours, or at least about 24 hours, when orally administered to a human patient.

[0029] In certain embodiments of the present invention the opioid antagonist present in the dosage form is present in a substantially non-releasable form (i.e., “sequestered”) when the dosage form is administered intact as directed. Preferably, because the opioid antagonist is present in the dosage form in a substantially non-releasable form, it does not substantially block the analgesic effect of the opioid agonist when the dosage form is orally administered intact, and does not pose a risk of precipitation of withdrawal in opioid tolerant or dependent patients.

[0030] In certain embodiments of the present invention, the aversive agent present in the dosage form is present in a substantially non-releasable form (i.e., “sequestered”) instead of, or in addition to, the opioid antagonist being in a substantially non-releasable form.

[0031] In other embodiments, the aversive agent may not be “sequestered” as disclosed above wherein the aversive agent is not released or minimally released from an intact dosage form, but may have a modified or sustained release so as not to dump the aversive agent in a particular section of the gastrointestinal tract; e.g. the stomach, where it may cause an unwanted effect such as excessive irritation. The aversive agent can be combined with an enteric carrier to delay its release or combined with a carrier to provide a sustained release of the aversive agent. However, it is contemplated in the present invention that the aversive agent will preferably not have any significant side effect (e.g., gastrointestinal side effect) even if all of the aversive agent is immediately released upon oral administration of an intact dosage form as directed. The aversive agent(s) can also be in the dosage form in releasable form and non-releasable form in any combination. For example, a dosage form can have a bittering agent, irritant, gel or combination thereof in releasable form and non-releasable form as disclosed in U.S. Patent Application entitled “Compositions And Methods To Prevent Abuse Of Opioids” filed Aug. 6, 2002. Likewise, the antagonist of the present invention may be in releasable form, non-releasable form or a combination of releasable form and non-releasable form as disclosed in U.S. Patent Application entitled “Pharmaceutical Formulations Containing Opioid Agonist, Releasable Antagonist, and Sequestered Antagonist” filed Aug. 6, 2002 and hereby incorporated by reference in its entirety, in combination with one of the aversive agents disclosed herein.

[0032] For example, the antagonist of the present invention can be an antagonist with minimal oral activity such as naloxone in releasable or “non-sequestered” form. The inclusion of such an antagonist would be a deterrent to parenteral abuse of the dosage form and the aversive agents of the present invention (i.e., bittering agent, irritant, gelling agent) would be a deterrent to oral and nasal abuse of the

dosage form. In addition, the dosage form can contain a "sequestered" antagonist such as a bioavailable antagonist to further deter the oral and nasal abuse of the dosage form upon administration of a tampered dosage form.

[0033] The term "aversive agent" is defined for purposes of the present invention to mean a bittering agent, an irritant, or a gelling agent.

[0034] The term "tampered dosage form" is defined for purposes of the present invention to mean that the dosage form has been manipulated by mechanical, thermal, and/or chemical means which changes the physical properties of the dosage form, e.g., to liberate the opioid agonist for immediate release if it is in sustained release form, or to make the opioid agonist available for inappropriate use such as administration by an alternate route, e.g., parenterally. The tampering can be, e.g., by means of crushing, shearing, grinding, chewing, dissolution in a solvent, heating, (e.g., greater than about 45° C.), or any combination thereof.

[0035] The term "substantially non-releasable form" for purposes of the present invention refers to an opioid antagonist and/or aversive agent that is not released or substantially not released at one hour after the intact dosage form containing an opioid agonist, an opioid antagonist and at least one aversive agent is orally administered (i.e., without having been tampered with). Formulations comprising an opioid antagonist in a dosage form in a substantially non-releasable form are described in U.S. application Ser. No. 09/781,081, entitled "Tamper Resistant Oral Opioid Agonist Formulations", filed Feb. 8, 2001, the disclosure of which is hereby incorporated by reference in its entirety. For purposes of the present invention, the amount released after oral administration of the intact dosage form may be measured in-vitro via the dissolution at 1 hour of the dosage form in 900 ml of Simulated Gastric Fluid using a USP Type II (paddle) apparatus at 75 rpm at 37° C. Such a dosage form is also referred to as comprising a "sequestered antagonist" and/or a "sequestered aversive agent" depending on the agent or agents which are not released or substantially not released. In certain preferred embodiments of the invention, the substantially non-releasable form of the antagonist and/or the aversive agent is resistant to laxatives (e.g., mineral oil) used to manage delayed colonic transit and resistant to achlorhydric states. Preferably, the aversive agent is not released or not substantially released 4, 8, 12 and/or 24 hours after oral administration.

[0036] The phrase "at least partially blocking the opioid effect", is defined for purposes of the present invention to mean that the opioid antagonist at least significantly blocks the euphoric effect of the opioid antagonist, thereby reducing the potential for abuse of the opioid agonist in the dosage form.

[0037] The phrase "analgesic effectiveness" is defined for purposes of the present invention as a satisfactory reduction in or elimination of pain, along with a tolerable level of side effects, as determined by the human patient.

[0038] The phrase "not substantially blocking the analgesic effect of an opioid agonist" for purposes of the present invention means that the opioid antagonist does not block the effects of the opioid agonist in sufficient degree as to render the dosage form therapeutically less effective for providing analgesia.

[0039] The term "sustained release" is defined for purposes of the present invention as the release of the opioid analgesic from the oral dosage form at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range but below toxic levels over an extended period of time, e.g., from about 12 to about 24 hours as compared to an immediate release product. Preferably the sustained release is sufficient to provide a twice-a-day or a once-a-day formulation.

[0040] The term "particles" of opioid antagonist, as used herein, refers to granules, spheroids, beads or pellets comprising the opioid antagonist. In certain preferred embodiments, the opioid antagonist particles are about 0.2 to about 2 mm in diameter, more preferably about 0.5 to about 2 mm in diameter.

[0041] The term "parenterally" as used herein includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, infusion techniques, or other methods of injection known in the art.

[0042] The term "inhaled" as used herein includes transmucosal, trans-bronchial, and trans-nasal abuse.

[0043] The term "bittering agent" as used herein includes a compound used to impart a bitter taste, bitter flavor, etc., to an abuser administering a tampered dosage form of the present invention.

[0044] The term "irritant" as used herein includes a compound used to impart an irritating, e.g., burning or uncomfortable, sensation to an abuser administering a tampered dosage form of the present invention.

[0045] The term "gelling agent" as used herein includes a compound or composition used to impart gel-like or thickening quality to a tampered dosage form upon the addition of moisture or liquid.

#### DETAILED DESCRIPTION OF THE INVENTION

[0046] The aversive agents of the present invention are preferably for use in connection with oral dosage forms including opioid analgesics and opioid antagonists, which provide valuable analgesia but which may be abused. This is particularly true for controlled release opioid analgesic products which have a large dose of a desirable opioid analgesic intended to be released over a period of time in each dosage unit. Drug abusers typically may take a controlled-release product and crush, shear, grind, chew, dissolve and/or heat, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption by injection, inhalation, and/or oral consumption.

[0047] In certain embodiments, the present invention comprises a method for preventing or deterring of the abuse of opioid analgesics by the inclusion of an opioid antagonist and at least one aversive agent in the dosage form with the opioid analgesic.

[0048] In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising a bittering agent, various bittering agents can be employed including, for example and without limitation, natural, artificial and synthetic flavor oils and flavoring aromatics and/or oils, oleoresins and extracts derived from

plants, leaves, flowers, fruits, and so forth, and combinations thereof. Nonlimiting representative flavor oils include spearmint oil, peppermint oil, eucalyptus oil, oil of nutmeg, allspice, mace, oil of bitter almonds, menthol and the like. Also useful bittering agents are artificial, natural and synthetic fruit flavors such as citrus oils including lemon, orange, lime, grapefruit, and fruit essences and so forth. Additional bittering agents include sucrose derivatives (e.g., sucrose octaacetate), chlorosucrose derivatives, quinine sulphate, and the like. The preferred bittering agent for use in the present invention is Denatonium Benzoate NF-Anhydrous, sold under the name Bitrex™ (Macfarlan Smith Limited, Edinburgh, UK).

[0049] With the inclusion of a bittering agent in the formulation, the intake of the tampered, with dosage form produces a bitter taste upon inhalation or oral administration which in certain embodiments spoils or hinders the pleasure of obtaining a high from the tampered dosage form, and preferably prevents the abuse of the dosage form.

[0050] A bittering agent may be added to the formulation in an amount of less than about 50% by weight preferably less than about 10% by weight, most preferably less than about 5% by weight of the dosage form, and most preferably in an amount ranging from about 0.1 to 1.0 percent by weight of the dosage form depending on the particular bittering agent(s) used. A dosage form including a bittering agent preferably discourages improper usage of the tampered dosage form by imparting a disagreeable taste or flavor to the tampered dosage form.

[0051] In certain embodiments of the present invention wherein the dosage form includes an aversive agent comprising an irritant, various irritants can be employed including, for example and without limitation capsaicin, a capsaicin analog with similar type properties as capsaicin, and the like. Some capsaicin analogues or derivatives include for example and without limitation, resiniferatoxin, tinyatoxin, heptanoylisobutylamide, heptanoyl guaiacylamide, other isobutylamides or guaiacylamides, dihydrocapsaicin, homovanillyl octylester, nonanoyl vanillylamide, or other compounds of the class known as vanilloids. Resiniferatoxin is described, for example, in U.S. Pat. No. 5,290,816 (Blumberg), issued Mar. 1, 1994. U.S. Pat. No. 4,812,446 (Brand), issued Mar. 14, 1989, describes capsaicin analogs and methods for their preparation. Further, U.S. Pat. No. 4,424,205 (LaHann et al.), issued Jan. 3, 1984, cite Newman, "Natural and Synthetic Pepper-Flavored Substances" published in 1954 as listing pungency of capsaicin-like analogs. Ton et al., *British Journal of Pharmacology*, 10, pp. 175-182 (1955) discuss pharmacological actions of capsaicin and its analogs.

[0052] With the inclusion of an irritant (e.g., capsaicin) in the dosage form, when the dosage form is tampered with, the capsaicin imparts a burning or discomforting quality to the abuser to preferably discourage the inhalation, injection, or oral administration of the tampered dosage form, and preferably to prevent the abuse of the dosage form. Suitable capsaicin compositions include capsaicin (trans 8-methyl-N-vanillyl-6-nonamide) or analogues thereof in a concentration between about 0.00125% and 50% by weight, preferably between about 1 and about 7.5% by weight, and most preferably, between about 1 and about 5% by weight.

[0053] In certain embodiments of the present invention wherein the dosage form includes an aversive agent com-

prising a gelling agent, various gelling agents can be employed including, for example and without limitation, sugars or sugar derived alcohols, such as mannitol, sorbitol, and the like, starch and starch derivatives, cellulose derivatives, such as microcrystalline cellulose, sodium carboxymethyl cellulose, methylcellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose, attapulgites, bentonites, dextrans, alginates, carrageenan, gum tragacanth, gum acacia, guar gum, xanthan gum, pectin, gelatin, kaolin, lecithin, magnesium aluminum silicate, the carbomers and carbopols, polyvinylpyrrolidone, polyethylene glycol, polyethylene oxide, polyvinyl alcohol, silicon dioxide, surfactants, mixed surfactant/wetting agent systems, emulsifiers, other polymeric materials, and mixtures thereof, etc. In certain preferred embodiments, the gelling agent is xanthan gum. In other preferred embodiments, the gelling agent of the present invention is pectin. The pectin or pectic substances useful for this invention include not only purified or isolated pectates but also crude natural pectin sources, such as apple, citrus or sugar beet residues which have been subjected, when necessary, to esterification or de-esterification, e.g., by alkali or enzymes. Preferably, the pectins used in this invention are derived from citrus fruits such as lime, lemon, grapefruit, and orange.

[0054] With the inclusion of a gelling agent in the dosage form, when the dosage form is tampered with, the gelling agent preferably imparts a gel-like quality to the tampered dosage form which preferably spoils or hinders the pleasure of obtaining a rapid high from the tampered dosage form due to the gel like consistency in contact with the mucous membrane, and in certain embodiments, prevents the abuse of the dosage form by minimizing absorption, e.g. in the nasal passages. A gelling agent may be added to the formulation in a ratio of gelling agent to opioid agonist of from about 1:40 to about 40:1 by weight, preferably from about 1:1 to about 30:1 by weight, and more preferably from about 2:1 to about 10:1 by weight of the opioid agonist.

[0055] In certain other embodiments, the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid (from about 0.5 to about 10 ml and preferably from 1 to about 5 ml), causing the resulting mixture to have a viscosity of at least about 10 cP. Most preferably, the resulting mixture will have a viscosity of at least about 60 cP.

[0056] In certain other embodiments, the dosage form forms a viscous gel after the dosage form is tampered with, dissolved in an aqueous liquid (from about 0.5 to about 10 ml and preferably from 1 to about 5 ml) and then heated (e.g., greater than about 45° C.), causing the resulting mixture to have a viscosity of at least about 10 cP. Most preferably, the resulting mixture will have a viscosity of at least about 60 cP.

[0057] In certain embodiments, the dosage form may include one or more of the aforementioned aversive agents. For safety reasons, the amount of the bittering agent, irritant, or gelling agent in the formulation of the present invention should not be toxic to humans.

[0058] Opioid antagonists useful in the present invention include, for example and without limitation, naltrexone, naloxone, nalmefene, nalide, nalmexone, nalorphine, nalorphine dinicotinate, cyclazocine, levallorphan, pharmaceuti-

cally acceptable salts thereof, and mixtures thereof. In certain preferred embodiments, the opioid antagonist is naloxone or naltrexone. In certain embodiments, the amount of the opioid antagonist included in the dosage form, may be about 10 ng to 275 mg.

[0059] Naloxone is an opioid antagonist which is almost void of agonist effects. Subcutaneous doses of up to 12 mg of naloxone produce no discernable subjective effects, and 24 mg naloxone causes only slight drowsiness. Small doses (0.4-0.8 mg) of naloxone given intramuscularly or intravenously in man prevent or promptly reverse the effects of morphine-like opioid agonist. One mg of naloxone intravenously has been reported to completely block the effect of 25 mg of heroin. The effects of naloxone are seen almost immediately after intravenous administration. The drug is absorbed after oral administration, but has been reported to be metabolized into an inactive form rapidly in its first passage through the liver such that it has been reported to have significantly lower potency than as when parenterally administered. Oral dosages of more than 1 g have been reported to be almost completely metabolized in less than 24 hours. It has been reported that 25% of naloxone administered sublingually is absorbed. Weinberg, et al., Sublingual Absorption of selected Opioid Analgesics, *Clin Pharmacol Ther.* (1988); 44:335-340.

[0060] Other opioid antagonists, for example, cyclazocine and naltrexone, both of which have cyclopropylmethyl substitutions on the nitrogen, retain much of their efficacy by the oral route and their durations of action are much longer, approaching 24 hours after their oral administration.

[0061] In the treatment of patients previously addicted to opioids, naltrexone has been used in large oral doses (over 100 mg) to prevent euphorogenic effects of opioid agonists. Naltrexone has been reported to exert strong preferential blocking action against mu over delta sites. Naltrexone is known as a synthetic congener of oxymorphone with no opioid agonist properties, and differs in structure from oxymorphone by the replacement of the methyl group located on the nitrogen atom of oxymorphone with a cyclopropylmethyl group. The hydrochloride salt of naltrexone is soluble in water up to about 100 mg/cc. The pharmacological and pharmacokinetic properties of naltrexone have been evaluated in multiple animal and clinical studies. See, e.g., Gonzalez J P, et al. Naltrexone: A review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy in the Management of Opioid Dependence. *Drugs* 1988; 35:192-213, hereby incorporated by reference. Following oral administration, naltrexone is rapidly absorbed (within 1 hour) and has an oral bioavailability ranging from 5-40%. Naltrexone's protein binding is approximately 21% and the volume of distribution following single-dose administration is 16.1 L/kg.

[0062] Naltrexone is commercially available in tablet form (Revia®, DuPont) for the treatment of alcohol dependence and for the blockade of exogenously administered opioids. See, e.g., Revia (naltrexone hydrochloride tablets). *Physician's Desk Reference* 51<sup>st</sup> ed., Montvale, N.J. "Medical Economics" 1997; 51:957-959. A dosage of 50 mg Revia® blocks the pharmacological effects of 25 mg IV administered heroin for up to 24 hours.

[0063] It is known that when coadministered with morphine, heroin or other opioids on a chronic basis, naltrexone

blocks the development of physical dependence to opioids. It is believed that the method by which naltrexone blocks the effects of heroin is by competitively binding at the opioid receptors. Naltrexone has been used to treat narcotic addiction by complete blockade of the effects of opioids. It has been found that the most successful use of naltrexone for a narcotic addiction is with narcotic addicts having good prognosis, as part of a comprehensive occupational or rehabilitative program involving behavioral control or other compliance enhancing methods. For treatment of narcotic dependence with naltrexone, it is desirable that the patient be opioid-free for at least 7-10 days. The initial dosage of naltrexone for such purposes has typically been about 25 mg, and if no withdrawal signs occur, the dosage may be increased to 50 mg per day. A daily dosage of 50 mg is considered to produce adequate clinical blockade of the actions of parenterally administered opioids. Naltrexone has also been used for the treatment of alcoholism as an adjunct with social and psychotherapeutic methods.

[0064] In certain embodiments, the aversive agent and/or the opioid antagonist included in the dosage form may be in a substantially non-releasable form. Where the opioid antagonist is in a substantially non-releasable form, the substantially non-releasable form of the opioid antagonist comprises an opioid antagonist that is formulated with one or more pharmaceutically acceptable hydrophobic materials, such that the antagonist is not released or substantially not released during its transit through the gastrointestinal tract when administered orally as intended, without having been tampered with.

[0065] Additionally, in certain embodiments, wherein the aversive agent is in a substantially non-releasable form, the substantially non-releasable form of the aversive agent comprises an aversive agent that is formulated with one or more pharmaceutically acceptable materials acceptable hydrophobic materials, such that the aversive agent is not released or substantially not released during its transit through the gastrointestinal tract when administered orally as intended, without having been tampered with.

[0066] In certain embodiments of the present invention, the substantially non-releasable form of the opioid antagonist is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating (e.g., greater than about 45° C.) of the oral dosage form. When the dosage form is tampered with, the integrity of the substantially non-releasable form of the opioid antagonist will be compromised, and the opioid antagonist will be made available to be released. In certain embodiments, when the dosage form is chewed, crushed or dissolved and heated in a solvent, and administered orally, intranasally, parenterally or sublingually, the analgesic or euphoric effect of the opioid is reduced or eliminated. In certain embodiments, the effect of the opioid agonist is at least partially blocked by the opioid antagonist. In certain other embodiments, the effect of the opioid agonist is substantially blocked by the opioid antagonist.

[0067] Additionally, the substantially non-releasable form of the aversive agent is vulnerable to mechanical, thermal and/or chemical tampering, e.g., tampering by means of crushing, shearing, grinding, chewing and/or dissolution in a solvent in combination with heating (e.g., greater than

about 45° C.) of the oral dosage form. When the dosage form is tampered with, the integrity of the substantially non-releasable form of the aversive agent will be compromised, and the aversive agent will be made available to be released. In certain embodiments, when the dosage form is chewed, crushed or dissolved and heated in a solvent, the release of the aversive agent hinders, deters or prevents the administration of the tampered dosage form orally, intranasally, parenterally and/or sublingually.

[0068] In certain embodiments of the present invention, ratio of the opioid agonist to the substantially non-releasable form of an opioid antagonist in the oral dosage form is such that the effect of the opioid agonist is at least partially blocked when the dosage form is chewed, crushed or dissolved in a solvent and heated, and administered orally, intranasally, parenterally or sublingually. Since the oral dosage form of certain embodiments described herein, when administered properly as intended, would not substantially release the opioid antagonist and/or the aversive agent, the amount of such antagonist and/or aversive agent may be varied more widely than if the opioid antagonist and/or aversive agent is available to be released into the gastrointestinal system upon oral administration. For safety reasons, the amount of the antagonist and/or aversive agent present in a substantially non-releasable form should not be harmful to humans even if fully released. The ratio of particular opioid agonist to antagonist can be determined without undue experimentation by one skilled in the art.

[0069] In certain embodiments of the present invention, the ratio of the opioid agonist and the opioid antagonist, present in a substantially non-releasable form, is about 1:1 to about 50:1 by weight, preferably about 1:1 to about 20:1 by weight. In certain preferred embodiments, the ratio is about 1:1 to about 10:1 by weight. In a preferred embodiment of the invention, the opioid agonist comprises oxycodone or hydrocodone and is present in the amount of about 15-45 mg and the opioid antagonist comprises naltrexone and is present in an amount of about 0.5 to about 10 mg, preferably about 0.5 to about 5 mg.

[0070] In an alternative embodiment, the opioid antagonist of the present invention may be included in the dosage form, such that it is analgesically effective when orally administered, but which upon parenteral administration, does not produce analgesia, euphoria or physical dependence. In this particular embodiment, preferably the opioid antagonist is naloxone which is in an amount which is not orally effective, but is parenterally effective, as described in U.S. Pat. No. 3,773,955, the disclosure of which is hereby incorporated by reference in its entirety. In this embodiment, the naloxone is released from the dosage form when orally administered, but does not abolish the oral activity of the opioid analgesic included in the dosage form.

[0071] Alternatively, the opioid antagonist of the present invention is released from the dosage form upon oral administration and may be included in the dosage form in an amount as described in WO 99/32119, the disclosure of which is hereby incorporated by reference in its entirety, (i) which does not cause a reduction in the level of analgesia elicited from the dosage form upon oral administration to a non-therapeutic level and (ii) which provides at least a mildly negative, "aversive" experience in physically dependent subjects (e.g., precipitated abstinence syndrome) when

the subjects attempt to take at least twice the usually prescribed dose at a time (and often 2-3 times that dose or more), as compared to a comparable dose of the opioid without the opioid antagonist present. Preferably, the amount of antagonist included in the oral dosage form is less positively reinforcing (e.g., less "liked") to a non-physically dependent opioid addict than a comparable oral dosage form without the antagonist included. Preferably, the formulation provides effective analgesia when orally administered. In certain preferred embodiments, the oral dosage form comprises an orally therapeutically effective dose of an opioid agonist, and an opioid antagonist in a ratio that provides a combination product which is analgesically effective when the combination is administered orally, but which is aversive in physically dependent human subjects when administered at the same dose or at a higher dose than said therapeutically effective dose.

[0072] Based on a preferred ratio of naltrexone in an amount from about 0.5 to about 4 mg per 15 mg of hydrocodone as described in WO 99/32119, the approximate ratio of naltrexone to 1 mg of certain opioids is set forth in Table A:

TABLE A

| Weight Ratio of Naltrexone per Dose Opioid |                                         |
|--------------------------------------------|-----------------------------------------|
| Opioid                                     | Weight Ratio Naltrexone per 1 mg Opioid |
| Oxycodone                                  | 0.037 to 0.296                          |
| Codeine                                    | 0.005 to 0.044                          |
| Hydrocodone                                | 0.033 to 0.267                          |
| Hydromorphone                              | 0.148 to 1.185                          |
| Levorphanol                                | 0.278 to 2.222                          |
| Meperidine                                 | 0.0037 to 0.0296                        |
| Methadone                                  | 0.056 to 0.444                          |
| Morphine                                   | 0.018 to 0.148                          |

[0073] Based on the more preferred ratio of about 0.75 mg to about 3 mg naltrexone per 15 mg hydrocodone of naltrexone as described in WO 99/32119, the approximate ratio of naltrexone to 1 mg of certain opioids is set forth in Table B below:

TABLE B

| Weight Ratio of Naltrexone per Dose Opioid |                         |
|--------------------------------------------|-------------------------|
| Opioid                                     | Weight Ratio Naltrexone |
| Oxycodone                                  | 0.056 to 0.222          |
| Codeine                                    | 0.0083 to 0.033         |
| Hydrocodone                                | 0.050 to 0.200          |
| Hydromorphone                              | 0.222 to 0.889          |
| Levorphanol                                | 0.417 to 1.667          |
| Meperidine                                 | 0.0056 to 0.022         |
| Methadone                                  | 0.083 to 0.333          |
| Morphine                                   | 0.028 to 0.111          |

[0074] In certain embodiments, the present invention is directed in part to an oral dosage form comprising an orally analgesically effective amount of an opioid agonist and an opioid antagonist in a ratios as described above along with one or more aversive agents as described herein.

[0075] In certain alternative embodiments, when the opioid antagonist is naloxone, the opioid agonist and antago-



nist (e.g., naloxone) included in the present dosage forms may be in preferred ratios as described in U.S. Pat. No. 4,457,933 to Gordon et al., the disclosure of which is hereby incorporated by reference in its entirety, such that both the oral and parenteral abuse potentials of the opioid agonist is diminished without appreciably affecting the oral analgetic activity of the opioid agonist.

[0076] In certain alternative embodiments, the opioid antagonist may be included in the dosage form in an amount such that the opioid antagonist attenuates side effects of the opioid agonist, said side effects being anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and combinations of any of the foregoing. For example, in certain preferred embodiments, the amount of the opioid antagonist is from about 100 to about 1000 fold less than the amount of the opioid agonist. Certain preferred amounts of opioid antagonist to agonist in accordance with this embodiment are described, for example, in U.S. Pat. Nos. 5,472,943; 5,512,578; 5,580,876; 5,767,125; RE36,547; and 6,096,256 all to Crain et al., the disclosures of which are herein incorporated by reference in their entireties.

[0077] All known combinations of releasable opioid antagonists with opioid agonists such as those described in U.S. Pat. No. 3,773,955 (Pachter, et al.); U.S. Pat. No. 3,493,657 (Lewenstein, et al.) U.S. Pat. No. 4,457,933 (Gordon, et al.); U.S. Pat. No. 4,582,835 (Lewis) U.S. Pat. Nos. 5,512,578; 5,472,943; 5,580,876; and 5,767,125 (Crain) and U.S. Pat. No. 4,769,372 and 4,785,000 (Kreek) can be combined with the aversive agents disclosed herein and all of these references are hereby incorporated by reference.

[0078] All commercial products of opioid agonist and releasable antagonists can be combined with an aversive agent disclosed herein. For example, Talwin NX can be formulated with an aversive agent, e.g., a bittering agent to reduce oral abuse as well as parenteral abuse of the opioid therein.

[0079] The opioid agonists useful in the present invention include, but are not limited to, alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydromorphone, dihydromorphone, dimenoxadol, dimepheptanol, dimethyltiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, etioheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, meptazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like. In certain embodiments, the amount of the opioid agonist in the claimed opioid composition may be about 75 ng to about 750 mg.

[0080] In certain preferred embodiments, the opioid agonist is selected from the group consisting of hydrocodone,

morphine, hydromorphone, oxycodone, codeine, levorphanol, meperidine, methadone, oxymorphone, buprenorphine, fentanyl and derivatives thereof, dipipanone, heroin, tramadol, etorphine, dihydroetorphine, butorphanol, levorphanol, or salts thereof or mixtures thereof. In certain preferred embodiments, the opioid agonist is oxycodone or hydrocodone.

[0081] In embodiments in which the opioid analgesic comprises hydrocodone, dosage forms may include analgesic doses from about 2 mg to about 50 mg of hydrocodone bitartrate. In embodiments in which the opioid analgesic comprises hydromorphone the dosage form may include from about 2 mg to about 64 mg hydromorphone hydrochloride. In embodiments in which the opioid analgesic comprises morphine, the dosage form may include from about 2.5 mg to about 800 mg morphine sulfate, by weight. In embodiments in which the opioid analgesic comprises oxycodone, the dosage form may include from about 2.5 mg to about 320 mg oxycodone hydrochloride. The dosage form may contain more than one opioid analgesic to provide a therapeutic effect. Alternatively, the dosage form may contain molar equivalent amounts of other salts of the opioids useful in the present invention.

[0082] Although hydrocodone and oxycodone are effective in the management of pain, there has been an increase in their abuse by individuals who are psychologically dependent on opioids or who misuse opioids for non-therapeutic reasons. Previous experience with other opioids has demonstrated a decreased abuse potential when opioids are administered in combination with a narcotic antagonist especially in patients who are ex-addicts. Weinhold L L, et al. Buprenorphine Alone and in Combination with Naltrexone in Non-Dependent Humans, *Drug and Alcohol Dependence* 1992; 30:263-274; Mendelson J., et al., Buprenorphine and Naloxone Interactions in Opiate-Dependent Volunteers, *Clin Pharm Ther.* 1996; 60:105-114; both of which are hereby incorporated by reference. These combinations, however, do not contain the opioid antagonist that is in a substantially non-releasable form. Rather, the opioid antagonist is released in the gastrointestinal system when orally administered and is made available for absorption, relying on the physiology of the host to differentially metabolize the agonist and antagonist and negate the agonist effects.

[0083] Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple central nervous system and gastrointestinal actions. Chemically, hydrocodone is 4,5-epoxy-3-methoxy-17-methylmorphinan-6-one, and is also known as dihydrocodeinone. Like other opioids, hydrocodone may be habit forming and may produce drug dependence of the morphine type. In excess doses hydrocodone, like other opium derivatives, will depress respiration.

[0084] Oral hydrocodone is also available in Europe (Belgium, Germany, Greece, Italy, Luxembourg, Norway and Switzerland) as an antitussive agent. A parenteral formulation is also available in Germany as an antitussive agent. For use as an analgesic, hydrocodone bitartrate is commercially available in the United States only as a fixed combination with non-opiate drugs (i.e., ibuprofen, acetaminophen, aspirin, etc.) for relief of moderate or moderately severe pain.

[0085] A common dosage form of hydrocodone is in combination with acetaminophen, and is commercially

available, e.g., as Lortab® in the U.S. from UCB Pharma, Inc. as 2.5/500 mg, 5/500 mg, 7.5/500 mg and 10/500 mg hydrocodone/acetaminophen tablets. Tablets are also available in the ratio of 7.5 mg hydrocodone bitartrate and 650 mg acetaminophen; and 7.5 mg hydrocodone bitartrate and 750 mg acetaminophen. Hydrocodone in combination with aspirin is given in an oral dosage form to adults generally in 1-2 tablets every 4-6 hours as needed to alleviate pain. The tablet form is 5 mg hydrocodone bitartrate and 224 mg aspirin with 32 mg caffeine; or 5 mg hydrocodone bitartrate and 500 mg aspirin. A relatively new formulation comprises hydrocodone bitartrate and ibuprofen. Vicoprofen®, commercially available in the U.S. from Knoll Laboratories, is a tablet containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen. The present invention is contemplated to encompass all such formulations, with the inclusion of the opioid antagonist particles coated with a coating that renders the antagonist substantially non-releasable.

**[0086]** Oxycodone, chemically known as 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, is an opioid agonist whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. The precise mechanism of its analgesic action is not known, but specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

**[0087]** Oxycodone is commercially available in the United States, e.g., as Oxycontin® from Purdue Pharma L.P. as controlled-release tablets for oral administration containing 10 mg, 20 mg, 40 mg or 80 mg oxycodone hydrochloride, and as OxyLR™, also from Purdue Pharma L.P., as immediate-release capsules containing 5 mg oxycodone hydrochloride. The present invention is contemplated to encompass all such formulations, with the inclusion of an opioid antagonist and one or more aversive agents.

#### PREPARATION OF AVERSIVE AGENT IN A SUBSTANTIALLY NON-RELEASABLE FORM

**[0088]** In certain embodiments of the present invention, an aversive agent in a substantially non-releasable form may be prepared by combining the aversive agent with one or more of a pharmaceutically acceptable hydrophobic material. For example, aversive agent particles may be coated with coating that substantially prevents the release of the aversive agent, the coating comprising the hydrophobic material(s). Another example would be an aversive agent that is dispersed in a matrix that renders the aversive agent substantially non-releasable, the matrix comprising the hydrophobic material(s). In certain embodiments, the pharmaceutically acceptable hydrophobic material comprises a cellulose polymer selected from the group consisting of ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate and cellulose triacetate. An example of ethylcellulose is one that has an ethoxy content of 44 to 55%. Ethylcellulose may be used in the form of an alcoholic solution. In certain other embodiments, the hydrophobic material comprises polylactic acid, polyglycolic acid or a co-polymer of the polylactic and polyglycolic acid.

**[0089]** In certain embodiments, the hydrophobic material may comprise a cellulose polymer selected from the group

consisting of cellulose ether, cellulose ester, cellulose ester ether, and cellulose. The cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than zero and up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a polymer selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono, di, and tricellulose alkanylates, mono, di, and tricellulose aroylates, and mono, di, and tricellulose alkenylates. Exemplary polymers include cellulose acetate having a D.S. and an acetyl content up to 21%; cellulose acetate having an acetyl content up to 32 to 39.8%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%.

**[0090]** More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2 to 45 and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylate having a D.S. of 2.9 to 3 such as cellulose triacetate, cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, and coesters of cellulose such as cellulose acetate butyrate, cellulose acetate octanoate butyrate and cellulose acetate propionate.

**[0091]** Additional cellulose polymers useful for preparing an aversive agent in a substantially non-releasable form include acetaldehyde dimethyl cellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, and cellulose acetate dimethylaminocellulose acetate.

**[0092]** Acrylic polymers useful for preparation of the aversive agent in a substantially non-releasable form include, but are not limited to, acrylic resins comprising copolymers synthesized from acrylic and methacrylic acid esters (e.g., the copolymer of acrylic acid lower alkyl ester and methacrylic acid lower alkyl ester) containing about 0.02 to 0.03 mole of a tri (lower alkyl) ammonium group per mole of the acrylic and methacrylic monomers used. An example of a suitable acrylic resin is a polymer manufactured by Rohm Pharma GmbH and sold under the Eudragit® RS trademark. Eudragit RS30D is preferred. Eudragit® RS is a water insoluble copolymer of ethyl acrylate (EA), methyl methacrylate (MM) and trimethylammoniummethyl methacrylate chloride (TAM) in which the molar ratio of TAM to the remaining components (EA and MM) is 1:40. Acrylic resins such as Eudragit® RS may be used in the form of an aqueous suspension.

**[0093]** In certain embodiments of the invention, the acrylic polymer may be selected from the group consisting of acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate)

copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate co-polymers.

**[0094]** When the aversive agent in a substantially non-releasable form comprises aversive agent particles coated with a coating that renders the aversive agent substantially non-releasable, and when a cellulose polymer or an acrylic polymer is used for preparation of the coating composition, suitable plasticizers, e.g., acetyl triethyl citrate and/or acetyl tributyl citrate may also be admixed with the polymer. The coating may also contain additives such as coloring agents, talc and/or magnesium stearate, which are well known in the coating art.

**[0095]** The coating composition may be applied onto the aversive agent particles by spraying it onto the particles using any suitable spray equipment known in the art. For example, a Wuster fluidized-bed system may be used in which an air jet, injected from underneath, fluidizes the coated material and effects drying while the insoluble polymer coating is sprayed on. The thickness of the coating will depend on the characteristics of the particular coating composition being used. However, it is well within the ability of one skilled in the art to determine by routine experimentation the optimum thickness of a particular coating required for a particular dosage form of the present invention.

**[0096]** The pharmaceutically acceptable hydrophobic material useful for preparing an aversive agent in a substantially non-releasable form includes a biodegradable polymer comprising a poly(lactic/glycolic acid) ("PLGA"), a polylactide, a polyglycolide, a polyanhydride, a polyorthoester, polycaprolactones, polyphosphazenes, polysaccharides, proteinaceous polymers, polyesters, polydioxanone, polygluconate, polylactic-acid-polyethylene oxide copolymers, poly(hydroxybutyrate), polyphosphoester or mixtures or blends of any of these.

**[0097]** In certain embodiments, biodegradable polymer comprises a poly(lactic/glycolic acid), a copolymer of lactic and glycolic acid, having molecular weight of about 2,000 to about 500,000 daltons. The ratio of lactic acid to glycolic acid is from about 100:0 to about 25:75, with the ratio of lactic acid to glycolic acid of 65:35 being preferred.

**[0098]** Poly(lactic/glycolic acid) may be prepared by the procedure set forth in U.S. Pat. No. 4,293,539 (Ludwig et al.), the disclosure of which is hereby incorporated by reference in its entirety. In brief, Ludwig prepares the copolymer by condensation of lactic acid and glycolic acid in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). The amount of catalyst is not critical to the polymerization, but typically is from about 0.01 to about 20 parts by weight relative to the total weight of combined lactic acid and glycolic acid. The polymerization reaction may be conducted without solvents at a temperature from about 100° C. to about 250° C. for about 48 to about 96 hours, preferably under a reduced pressure to facilitate removal of water and by-products. Poly(lactic/glycolic acid) is then recovered by filtering the molten reaction mixture in an organic solvent such as dichloromethane or acetone and then filtering to remove the catalyst.

**[0099]** Once the aversive agent in a substantially non-releasable form is prepared, it may be combined with an

opioid agonist and the opioid antagonist (which may also be in a substantially non-releasable form as described herein), along with conventional excipients known in the art, to prepare the oral dosage form of the present invention. It is contemplated that a bittering agent or capsaicin would be the most likely aversive agents to be included in a sequestered formulation. The polymers and other ingredients above may also be utilized to formulate the aversive agents to slow release or delay release as disclosed above.

**[0100]** In certain preferred embodiments of the invention, the oral dosage form is a capsule or a tablet. When being formulated as a tablet, the aversive agent and opioid agonist and opioid antagonist may be combined with one or more inert, non-toxic pharmaceutical excipients which are suitable for the manufacture of tablets. Such excipients include, for example, an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate.

**[0101]** The oral dosage form of the present invention may be formulated to provide immediate release of the opioid agonist contained therein. In other embodiments of the invention, however, the oral dosage form provides sustained-release of the opioid agonist.

**[0102]** In certain embodiments, the oral dosage forms providing sustained release of the opioid agonist may be prepared by admixing the aversive agent in a substantially non-releasable form with the opioid agonist and the opioid antagonist and desirable pharmaceutical excipients to provide a tablet, and then coating the tablet with a sustained-release tablet coating.

**[0103]** In certain embodiments of the invention, sustained release opioid agonist tablets may be prepared by admixing the substantially non-releasable form of an aversive agent with an aversive agent in a matrix that provides the tablets with sustained-releasing properties.

## DOSAGE FORMS

**[0104]** The opioid analgesic/opioid antagonist formulation in combination with one or more aversive agents can be formulated as an immediate release formulation or controlled release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The controlled release dosage form may include a controlled release material which is incorporated into a matrix along with the opioid analgesic and the opioid antagonist. In addition, the aversive agent may be separate from the matrix, or incorporated into the matrix.

**[0105]** The controlled release dosage form may optionally comprise particles containing or comprising the opioid analgesic, wherein the particles have diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. The opioid antagonist may be incorporated into these particles, or may be incorporated into a tablet or capsule containing these particles. Additionally, the aversive agent may be incorporated into these particles, or may be incorporated into a tablet or capsule containing these particles. Preferably, the particles are film coated with a material that permits release of the opioid analgesic at a controlled rate in an environment of use. The film coat is chosen so as to achieve, in combination with the other stated properties, a

desired in-vitro release rate. The controlled release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

[0106] In certain embodiments, the dosage forms of the present invention comprise normal release matrixes containing the opioid analgesic, opioid antagonist, and the aversive agent.

#### COATED BEADS

[0107] In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads comprising an opioid analgesic, and a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. The beads comprising the opioid analgesic may further comprise the opioid antagonist and/or one or more aversive agents, or the opioid antagonist and or one or more aversive agents may be prepared as separate beads and then combined in a dosage form including the controlled release beads comprising an opioid analgesic, or the opioid antagonist and/or one or more aversive agents may be mixed in the dosage form with the controlled release beads comprising the opioid analgesic. In preferred embodiments where the opioid analgesic and the aversive agent are mixed in a capsule as different beads, the beads have an exact or similar appearance in order to deter an abuser from manually separating the beads prior to abuse in order to avoid the aversive substance. In tablet dosage forms, the aversive agent is preferably not included as a distinct layer which can be easier to separate from the active agent, although the present invention does encompass these embodiments.

[0108] The controlled release bead formulations of the present invention slowly release the opioid analgesic, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

[0109] Spheroids or beads coated with an opioid analgesic are prepared, e.g., by dissolving the opioid analgesic in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wurster insert. Thereafter, the opioid antagonist and/or aversive agent is optionally added to the beads prior to coating. Optionally, additional ingredients are also added prior to coating the beads. For example, a product which includes hydroxypropylmethylcellulose, etc. (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated

substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the opioid analgesic from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

[0110] The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit® can be used.

[0111] Plasticized hydrophobic material may be applied onto the substrate comprising the opioid analgesic by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of said opioid analgesic when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the opioid analgesic, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

[0112] The release of the opioid analgesic from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

[0113] The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

[0114] The controlled release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

[0115] The controlled release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

[0116] The release-modifying agent may also comprise a semi-permeable polymer.

[0117] In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

[0118] The controlled release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864. The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

#### MATRIX FORMULATIONS

[0119] In certain embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a controlled release coating as set forth herein. The present invention may also utilize a sustained release matrix that affords in-vitro dissolution rates of the opioid analgesic and/or antagonist within desired ranges and releases the opioid analgesic and/or antagonist in a pH-dependent or pH-independent manner.

[0120] A non-limiting list of suitable sustained-release materials which may be included in a sustained-release matrix according to the invention includes hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil and hydrogenated vegetable oil. However, any pharmaceutically acceptable hydrophobic or hydrophilic sustained-release material which is capable of imparting sustained-release of the opioid analgesic may be used in accordance with the present invention. Preferred sustained-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers; and cellulose ethers, especially hydroxyalkylcelluloses (especially hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, ethyl acrylate, trimethyl ammonioethyl methacrylate, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methylmethacrylate), poly(methacrylic acid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Certain preferred embodiments utilize mixtures of any of the foregoing sustained-release materials in the matrix of the invention.

[0121] The matrix also may include a binder. In such embodiments, the binder preferably contributes to the sustained-release of the oxycodone or pharmaceutically acceptable salt thereof from the sustained-release matrix.

[0122] If an additional hydrophobic binder material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive. In certain preferred embodiments, a combination of two or more hydrophobic binder materials are included in the matrix formulations.

[0123] Preferred hydrophobic binder materials which may be used in accordance with the present invention include

digestible, long chain ( $C_8$ - $C_{50}$ , especially  $C_{12}$ - $C_{40}$ ), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols. Hydrocarbons having a melting point of between  $25^\circ$  and  $90^\circ$  C are preferred. Of the long-chain hydrocarbon binder materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 80% (by weight) of at least one digestible, long chain hydrocarbon.

[0124] In certain embodiments, the hydrophobic binder material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about  $30^\circ$  to about  $100^\circ$  C. In certain preferred embodiments, the dosage form comprises a sustained release matrix comprising an opioid analgesic; opioid antagonist; one or more aversive agents; and at least one water soluble hydroxyalkyl cellulose, at least one  $C_{12}$ - $C_{36}$ , preferably  $C_{14}$ - $C_{22}$ , aliphatic alcohol and, optionally, at least one polyalkylene glycol. The hydroxyalkyl cellulose is preferably a hydroxy ( $C_1$  to  $C_6$ ) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form may be determined, inter alia, by the precise rate of opioid analgesic release required. The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the aliphatic alcohol in the present oral dosage form may be determined, as above, by the precise rate of opioid analgesic release required. It may also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between about 20% and about 50% (by wt) of the aliphatic alcohol. When a polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol preferably constitutes between about 20% and about 50% (by wt) of the total dosage form.

[0125] In one preferred embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the opioid analgesic from the formulation. In certain embodiments, a ratio of the hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:1 and 1:4 is preferred, with a ratio of between 1:2 and 1:3 being particularly preferred.

[0126] In certain embodiments, the polyalkylene glycol may be, for example, polypropylene glycol, or polyethylene glycol which is preferred. The average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000, especially between 1,500 and 12,000.

[0127] Another suitable sustained-release matrix comprises an alkylcellulose (especially ethylcellulose), a C<sub>12</sub> to C<sub>36</sub> aliphatic alcohol and, optionally, a polyalkylene glycol.

[0128] In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids and glidants that are conventional in the pharmaceutical art.

[0129] In order to facilitate the preparation of a solid, sustained-release oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, sustained-release oral dosage form according to the present invention comprising incorporating an opioid analgesic in a sustained-release matrix. Incorporation in the matrix may be effected, for example, by:

[0130] (a) forming granules comprising at least one hydrophobic and/or hydrophilic material as set forth above (e.g., a water soluble hydroxyalkyl cellulose) together with the opioid analgesic, opioid antagonist, and at least one aversive agent;

[0131] (b) mixing the at least one hydrophobic and/or hydrophilic material-containing granules with at least one C<sub>12</sub>-C<sub>36</sub> aliphatic alcohol, and

[0132] (c) optionally, compressing and shaping the granules.

[0133] The granules may be formed by any of the procedures well-known to those skilled in the art of pharmaceutical formulation. For example, in one preferred method, the granules may be formed by wet granulating the hydroxyalkyl cellulose, opioid analgesic, opioid antagonist, and one or more aversive agents with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the opioid analgesic. Optionally, the opioid analgesic, opioid antagonist, and/or the one or more aversive agents are added extragranularly.

[0134] A sustained-release matrix can also be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g., a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate a hydrophobic sustained-release material, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material. Examples of sustained-release formulations prepared via melt-granulation techniques are found, e.g., in U.S. Pat. No. 4,861,598.

[0135] The additional hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve sustained release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like binder substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

[0136] The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the opioid analgesic, opioid antagonist, and at least one aversive agent, together with a sustained release material and preferably a binder material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The matrix multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the oxycodone or pharmaceutically acceptable salt thereof for a time period of at least about 24 hours.

[0137] An optional process for preparing the melt extruded formulations of the present invention includes directly metering into an extruder a hydrophobic sustained release material, the opioid analgesic, opioid antagonist, one or more aversive agents, and an optional binder material; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into matrix multiparticulates having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

[0138] Optionally, the opioid antagonist and/or the one or more aversive agents may be prepared as separate multiparticulates (without the opioid agonist) and thereafter the multiparticulates may be combined with multiparticulates comprising opioid analgesic (without the antagonist and/or the one or more aversive agents) in a dosage form.

[0139] Plasticizers, such as those described above, may be included in melt-extruded matrices. The plasticizer is preferably included as from about 0.1 to about 30% by weight of the matrix. Other pharmaceutical excipients, e.g., talc, mono or poly saccharides, lubricants and the like may be included in the sustained release matrices of the present invention as desired. The amounts included will depend upon the desired characteristic to be achieved.

[0140] The diameter of the extruder aperture or exit port can be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

[0141] A melt extruded matrix multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded matrix multiparticulate(s)" and "melt-extruded matrix multiparticulate system(s)" and "melt-extruded matrix particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic sustained release material as described herein. Preferably the melt-extruded matrix multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm. In addition, it is to be understood that the melt-extruded matrix multiparticulates can be any geometrical shape within this size range.



In certain embodiments, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

[0142] In one preferred embodiment, oral dosage forms are prepared that include an effective amount of melt-extruded matrix multiparticulates within a capsule. For example, a plurality of the melt-extruded matrix multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastrointestinal fluid.

[0143] In another embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in *Remington's Pharmaceutical Sciences*, (Arthur Osol, editor), 1553-1593 (1980).

[0144] In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681 (Klimesch, et. al.).

[0145] Optionally, the sustained-release matrix multiparticulate systems, tablets, or capsules can be coated with a sustained release coating such as the sustained release coatings described herein. Such coatings preferably include a sufficient amount of hydrophobic and/or hydrophilic sustained-release material to obtain a weight gain level from about 2 to about 25 percent, although the overcoat may be greater depending upon, e.g., the desired release rate. The coating can optionally contain one or more of the aversive agents. In such embodiments, an optional second overcoat can be applied as to minimize the perception of the aversive agent when a dosage form of the present inventions administered intact.

[0146] The dosage forms of the present invention may further include combinations of melt-extruded matrix multiparticulates containing an opioid analgesic; an opioid antagonist; one or more aversive agents; or mixtures thereof. Furthermore, the dosage forms can also include an amount of an immediate release opioid analgesic for prompt therapeutic effect. The immediate release opioid analgesic may be incorporated, e.g., as separate multiparticulates within a gelatin capsule, or may be coated on the surface of, e.g., melt extruded matrix multiparticulates.

[0147] The sustained-release profile of the melt-extruded formulations if the invention can be altered, for example, by varying the amount of sustained-release material, by varying the amount of plasticizer relative to other matrix constituents, by varying the amount of hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

[0148] In other embodiments of the invention, melt-extruded formulations are prepared without the inclusion of the opioid analgesic; opioid antagonist; one or more aversive agents; or mixtures thereof; which is added thereafter to the extrudate. Such formulations typically will have the opioid analgesic; opioid antagonist; one or more aversive agents; or mixtures thereof blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the opioid analgesic;

opioid antagonist; one or more aversive agents; or mixtures thereof included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

[0149] Typical melt-extrusion production systems suitable for use in accordance with the present invention include a suitable extruder drive motor having variable speed and constant torque control, start-stop controls, and a meter. In addition, the production system will include a temperature control console which includes temperature sensors, cooling means and temperature indicators throughout the length of the extruder. In addition, the production system will include an extruder such as a twin-screw extruder which consists of two counter-rotating intermeshing screws enclosed within a cylinder or barrel having an aperture or die at the exit thereof. The feed materials enter through a feed hopper and are moved through the barrel by the screws and are forced through the die into strands which are thereafter conveyed such as by a continuous movable belt to allow for cooling and being directed to a pelletizer or other suitable device to render the extruded ropes into the matrix multiparticulate system. The pelletizer can consist of rollers, fixed knife, rotating cutter and the like. Suitable instruments and systems are available from distributors such as C.W. Brabender Instruments, Inc. of South Hackensack, N.J. Other suitable apparatus will be apparent to those of ordinary skill in the art.

[0150] A further aspect of the invention is related to the preparation of melt-extruded matrix multiparticulates as set forth above in a manner which controls the amount of air included in the extruded product. By controlling the amount of air included in the extrudate, the release rate of the opioid analgesic, opioid antagonist, one or more aversive agents, or mixtures thereof may be altered.

[0151] Thus, in a further aspect of the invention, the melt-extruded product is prepared in a manner which substantially excludes air during the extrusion phase of the process. This may be accomplished, for example, by using a Leistritz extruder having a vacuum attachment. The extruded matrix multiparticulates prepared according to the invention using the Leistritz extruder under vacuum provides a melt-extruded product having different physical characteristics. In particular, the extrudate is substantially non-porous when magnified, e.g., using a scanning electron microscope which provides an SEM (scanning electron micrograph). Such substantially non-porous formulations may provide a faster release of the therapeutically active agent, relative to the same formulation prepared without vacuum. SEMs of the matrix multiparticulates prepared using an extruder under vacuum appear very smooth, and the multiparticulates tend to be more robust than those multiparticulates prepared without vacuum. It has been observed that in at least certain formulations, the use of extrusion under vacuum provides an extruded matrix multiparticulate product which is more pH-dependent than its counterpart formulation prepared without vacuum.

[0152] Alternatively, the melt-extruded product is prepared using a Werner-Pfleiderer twin screw extruder.

[0153] In certain embodiments, a spheronizing agent is added to a granulate or matrix multiparticulate and then spheronized to produce sustained release spheroids. The spheroids are then optionally overcoated with a sustained release coating by methods such as those described above.

[0154] Spheronizing agents which may be used to prepare the matrix multiparticulate formulations of the present invention include any art-known spheronizing agent. Cellulose derivatives are preferred, and microcrystalline cellulose is especially preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade-Mark, FMC Corporation). The spheronizing agent is preferably included as about 1 to about 99% of the matrix multiparticulate by weight.

[0155] In certain embodiments, in addition to the opioid analgesic, opioid antagonist, one or more aversive agents, and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

[0156] In certain embodiments, a sustained release coating is applied to the sustained release spheroids, granules, or matrix multiparticulates. In such embodiments, the sustained-release coating may include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein. The coating is preferably derived from an aqueous dispersion of the hydrophobic sustained release material.

[0157] In certain embodiments, it is necessary to overcoat the sustained release spheroids, granules, or matrix multiparticulates comprising the opioid analgesic, opioid antagonist, one or more aversive agents, and sustained release carrier with a sufficient amount of the aqueous dispersion of, e.g., alkylcellulose or acrylic polymer, to obtain a weight gain level from about 2 to about 50%, e.g., about 2 to about 25%, in order to obtain a sustained-release formulation. The overcoat may be lesser or greater depending upon, e.g., the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same. Cellulosic materials and polymers, including alkylcelluloses, are sustained release materials well suited for coating the sustained release spheroids, granules, or matrix multiparticulates according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

[0158] One commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

[0159] Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporat-

ing plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly to the sustained release spheroids, granules, or matrix multiparticulates.

[0160] In other preferred embodiments of the present invention, the sustained release material comprising the sustained-release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0161] In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in the National Formulary (NF) XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

[0162] Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm GmbH and Co. Kg Darmstadt, Germany. There are several different types of Eudragit®. For example, Eudragit E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit RL and Eudragit RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent; however, dosage forms coated with Eudragit RL and RS are pH-independent.

[0163] In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in



digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

[0164] The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained-release formulation having a desirable dissolution profile. Desirable sustained-release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L. In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic sustained release material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained-release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained-release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

[0165] Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

[0166] Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

[0167] In certain embodiments, the uncoated/coated sustained release spheroids, granules, or matrix multiparticulates containing the opioid analgesic; opioid antagonist; and one or more aversive agents; are cured until an endpoint is reached at which the sustained release spheroids, granules, or matrix multiparticulates provide a stable dissolution of the opioid. The curing endpoint may be determined by comparing the dissolution profile (curve) of the dosage form immediately after curing to the dissolution profile (curve) of the dosage form after exposure to accelerated storage conditions of, e.g., at least one month at a temperature of 40° C. and a relative humidity of 75%. Cured formulations are described in detail in U.S. Pat. Nos. 5,273,760; 5,286,493;

5,500,227; 5,580,578; 5,639,476; 5,681,585; and 6,024,982. Other examples of sustained-release formulations and coatings which may be used in accordance with the present invention include those described in U.S. Pat. Nos. 5,324,351; 5,356,467; and 5,472,712.

[0168] In addition to the above ingredients, the spheroids, granules, or matrix multiparticulates may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the formulation if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

[0169] Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association (1986), incorporated by reference herein.

[0170] It has further been found that the addition of a small amount of talc to the sustained release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

#### OSMOTIC DOSAGE FORMS

[0171] Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the opioid analgesic and optionally the opioid antagonist and/or one or more aversive agents) and a delivery c: push layer (which may contain the opioid antagonist and/or one or more aversive agents), wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

[0172] The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which the opioid analgesic (with or without the antagonist) can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the sustained metered release of opioid analgesic from the dosage form. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in U.S. Pat. Nos. 4,200,098 and 4,285,987.

**[0173]** In certain embodiments, the bilayer core comprises a drug layer with opioid analgesic and a displacement or push layer optionally containing the antagonist and/or one or more aversive agents. The antagonist and/or one or more aversive agents may optionally be included in the drug layer instead of or in addition to being included in the push layer. In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula  $(C_6H_{12}O_5)_n \cdot H_2O$ , wherein  $n$  is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

**[0174]** In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the contents of the drug layer from the osmotic dosage form.

**[0175]** The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulfate,

lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, glucose, fructose and maltose.

**[0176]** The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkylcellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropyl isopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

**[0177]** The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-di-tertiary butylphenol, alfatocopherol, and propylgallate.

**[0178]** In certain alternative embodiments, the dosage form comprises a substantially homogenous core comprising opioid analgesic, an opioid antagonist, one or more aversive agents, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The substantially homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the opioid analgesic, the opioid antagonist, and the one or more aversive agents.

**[0179]** In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkynylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

**[0180]** Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethylcellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,876; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable crosslinked polystyrenes; semipermeable crosslinked poly(sodium styrene sulfonate); semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride); and semipermeable polymers possessing a fluid permeability of  $2.5 \times 10^{-8}$  to  $2.5 \times 10^{-2}$  (cm<sup>2</sup>/hr-atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present invention are known in the art

in U.S. Pat. Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

[0181] In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it, maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinyl-caprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

[0182] In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

#### TRANSDERMAL DELIVERY SYSTEMS

[0183] The formulations of the present invention may be formulated as a transdermal delivery system, such as transdermal patches. In certain embodiments of the present invention, a transdermal patch comprises an opioid agonist contained in a reservoir or a matrix, and an adhesive which allows the transdermal device to adhere to the skin, allowing the passage of the active agent from the transdermal device through the skin of the patient, with the inclusion of the aversive agents and opioid antagonists as disclosed herein which are not releasable when the dosage form is administered intact but which are releasable when the dosage form is broken or tampered with in order to release the opioid from the transdermal system.

[0184] Transdennal delivery system providing a controlled-release of an opioid agonist is known. For example, Duragesic® patch (commercially available from Janssen Pharmaceutical) contains an opioid agonist (fentanyl) and is said to provide adequate analgesia for up to 48 to 72 hours (2 to 3 days). This formulation can be reformulated with an aversive agent and antagonist as disclosed herein.

[0185] There are several types of transdermal formulations of buprenorphine reported in the literature. See, for example, U.S. Pat. No. 5,240,711 (Hille et al.), U.S. Pat. No. 5,225,199 (Hidaka et al.), U.S. Pat. No. 5,069,909 (Sharma et al.), U.S. Pat. No. 4,806,341 (Chien et al.), and U.S. Pat. No. 5,026,556 (Drust et al.), all of which are hereby incorporated by reference. These transdermal devices can also be reformulated with the aversive agents and antagonists as disclosed herein.

[0186] The transdermal delivery system used in the present invention may also be prepared in accordance with

U.S. Pat. No. 5,069,909 (Sharma et al.), hereby incorporated by reference. This patent describes a laminated composite for administering buprenorphine transdermally to treat pain. The transdermal delivery system used in the present invention may also be prepared in accordance with U.S. Pat. No. 4,806,341 (Chien et al.), hereby incorporated by reference. This patent describes a transdermal morphinan narcotic analgesic or antagonist (including buprenorphine) pharmaceutical polymer matrix dosage unit having a backing layer which is substantially impervious to the buprenorphine, and a polymer matrix disc layer which is adhered to the backing layer and which has microdispersed therein effective dosage amounts of the buprenorphine.

[0187] The transdermal delivery system used in the present invention may also be that described in U.S. Pat. No. 5,026,556 (Drust et al.), hereby incorporated by reference. Therein, compositions for the transdermal delivery of buprenorphine comprise buprenorphine in a carrier of a polar solvent material selected from the group consisting of C<sub>3</sub>-C<sub>4</sub> diols, C<sub>3</sub>-C<sub>6</sub> triols, and mixtures thereof, and a polar lipid material selected from the group consisting of fatty alcohol esters, fatty acid esters, and mixtures thereof; wherein the polar solvent material and the lipid material are present in a weight ratio of solvent material:lipid material of from 60:40 to about 99:1. The transdermal delivery system used in the present invention may also be that described in U.S. Pat. No. 4,588,580 (Gale, et. al.), hereby incorporated by reference. That system comprises a reservoir for the drug having a skin proximal, material releasing surface area in the range of about 5-100 cm<sup>2</sup> and containing between 0.1 and 50% by weight of a skin permeable form of the buprenorphine. The reservoir contains an aqueous gel comprising up to about 47-95% ethanol, 1-10% gelling agent, 0.1-10% buprenorphine, and release rate controlling means disposed in the flow path of the drug to the skin which limits the flux of the buprenorphine from the system through the skin.

[0188] The transdermal delivery system used in the present invention may also be that described in PCT/US01/04347 to Oshlack et al.

[0189] The present invention is contemplated to encompass all transdermal formulations, e.g., the technologies described above, with the inclusion of an aversive agent and antagonist, such that the dosage form deters abuse of the opioid therein.

[0190] The aversive agent and antagonist in non-releasable form when administered intact can be formulated in accordance with U.S. Pat. No. 5,149,538 to Granger, hereby incorporated by reference. Alternatively, the aversive agent and the opioid agonist can be separated from the opioid by a layer which becomes disrupted when the dosage form is tampered with, thereby mixing the aversive agent with the opioid agonist. Alternatively, a combination of both systems can be used.

#### SUPPOSITORIES

[0191] The controlled release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising an opioid analgesic, opioid antagonist, and at least one aversive agent in a controlled release matrix, and a suppository vehicle (base). Preparation of controlled release suppository formulations is described in, e.g., U.S. Pat. No. 5,215,758.

[0192] The suppository base chosen should be compatible with the agent(s) of the present invention. Further, the suppository base is preferably non-toxic and nonirritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

[0193] In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural fatty acids of the chain length  $C_{12}$  to  $C_{18}$ .

[0194] In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

[0195] Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata TM (types AB, AB, B, BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witapol TM (types H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

[0196] Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of base (e.g., alginate) and drug used. Generally, the amount of suppository base is from about 20 percent to about 90 percent by weight of the total weight of the suppository. Preferably, the amount of base in the suppository is from about 65 percent to about 80 percent, by weight of the total weight of the suppository.

[0197] In certain embodiments of the dosage forms of the present invention may also include a surfactant. Surfactants useful in accordance with the present invention, include for example, ionic and nonionic surfactants or wetting agents commonly used in the formulation of pharmaceuticals, including but not limited to castor oil derivatives, cholesterol, polyglycolized glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, polysorbates, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene compounds, monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, sodium docusate, sodium laurylsulfate, cholic acid or derivatives thereof, ethoxylated alcohols, ethoxylated esters, ethoxylated amides, polyoxypropylene compounds, propoxylated alcohols, ethoxylated/propoxylated block polymers, propoxylated esters, alkanolamides, amine oxides, fatty acid esters of polyhydric alcohols, ethylene glycol esters, diethylene glycol esters, propylene glycol esters, glycerol esters, polyglycerol fatty acid esters, SPAN's (e.g., sorbitan esters), TWEEN's (i.e., sucrose esters), glucose (dextrose) esters, alkali metal sulfates, quaternary ammonium compounds, amidoamines, and aminimides, simethicone, lecithins, alcohols, phospholipids, and mixtures thereof.

[0198] Mixed surfactant/wetting agents useful in accordance with the present invention include, for example,

sodium lauryl sulfate/polyethylene glycol (PEG) 6000 and sodium lauryl sulfate/PEG 6000/stearic acid, etc.

[0199] In certain embodiments of the present invention, the dosage form may also include an emulsifying agent. Emulsifying agents useful in accordance with the present invention include, for example, monoglycerides, sucrose/fatty acid esters, polyglycerol/fatty acid esters, sorbitan/fatty acid esters, lecithins, potassium and sodium salts of rosin acids and higher fatty acids, as well as sulfates and sulfonates of these acids, amine salts of hydroxylamines of long-chain fatty acid esters, quaternary ammonium salts such as stearyl-dimethylbenzylammonium chloride and tridecylbenzenedihydroxyethylimidazole chloride, phosphoric esters of higher alcohols such as capryl and octyl alcohol, and monoesters of oleic acid and pentaerythritol such as sorbitan monooleates, and mixtures thereof.

[0200] The oral dosage form and methods for use of the present invention may further include, in addition to an opioid analgesic and opioid antagonist, one or more drugs that may or may not act synergistically with the opioid analgesic. Thus, in certain embodiments, a combination of two opioid analgesics may be included in the dosage form. For example, the dosage form may include two opioid analgesics having different properties, such as half-life, solubility, potency, and a combination of any of the foregoing.

[0201] In yet further embodiments, one or more opioid analgesic is included and a further non-opioid drug is also included. Such non-opioid drugs would preferably provide additional analgesia, and include, for example, aspirin, acetaminophen; non-steroidal anti-inflammatory drugs ("NSAIDs"), e.g., ibuprofen, ketoprofen, etc.; N-methyl-D-aspartate (NMDA) receptor antagonists, e.g., a morphinan such as dextromethorphan or dextrorphan, or ketamine; cyclooxygenase-II inhibitors ("COX-II inhibitors"); and/or glycine receptor antagonists.

[0202] In certain preferred embodiments of the present invention, the invention allows for the use of lower doses of the opioid analgesic by virtue of the inclusion of an additional non-opioid analgesic, such as an NSAID or a COX-2 inhibitor. By using lower amounts of either or both drugs, the side effects associated with effective pain management in humans are reduced.

[0203] Suitable non-steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, buclocic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acetaminacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflusal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Useful dosages of these drugs are well known to those skilled in the art.

[0204] N-methyl-D-aspartate (NMDA) receptor antagonists are well known in the art, and encompass, for example, morphinans such as dextromethorphan or dextrorphan, ketamine, or pharmaceutically acceptable salts thereof. For purposes of the present invention, the term "NMDA antagonist" is also deemed to encompass drugs that block a major

intracellular consequence of NMDA-receptor activation, e.g. a ganglioside such as GM<sub>1</sub> or GT<sub>1b</sub>, a phenothiazine such as trifluoperazine or a naphthalenesulfonamide such as N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide. These drugs are stated to inhibit the development of tolerance to and/or dependence on addictive drugs, e.g., narcotic analgesics such as morphine, codeine, etc. in U.S. Pat. Nos. 5,321,012 and 5,556,838 (both to Mayer, et al.), and to treat chronic pain in U.S. Pat. No. 5,502,058 (Mayer, et al.), all of which are hereby incorporated by reference. The NMDA antagonist may be included alone, or in combination with a local anesthetic such as lidocaine, as described in these Mayer, et.al. patents.

[0205] The treatment of chronic pain via the use of glycine receptor antagonists and the identification of such drugs is described in U.S. Pat. No. 5,514,680 (Weber, et al.).

[0206] COX-2 inhibitors have been reported in the art and many chemical structures are known to produce inhibition of cyclooxygenase-2. COX-2 inhibitors are described, for example, in U.S. Pat. Nos. 5,616,601; 5,604,260; 5,593,994; 5,550,142; 5,536,752; 5,521,213; 5,474,995; 5,639,780; 5,604,253; 5,552,422; 5,510,368; 5,436,265; 5,409,944; and 5,130,311, all of which are hereby incorporated by reference. Certain preferred COX-2 inhibitors include celecoxib (SC-58635), DUP-697, flosulide (CGP-28238), meloxicam, 6-methoxy-2-naphthylacetic acid (6-MNA), MK-966 (also known as Vioxx), nabumetone (prodrug for 6-MNA), nimesulide, NS-398, SC-5766, SC-58215, T-614; or combinations thereof. Dosage levels of COX-2 inhibitor on the order of from about 0.005 mg to about 140 mg per kilogram of body weight per day are therapeutically effective in combination with an opioid analgesic. Alternatively, about 0.25 mg to about 7 g per patient per day of a COX-2 inhibitor is administered in combination with an opioid analgesic.

[0207] In yet further embodiments, a non-opioid drug can be included which provides a desired effect other than analgesia, e.g., antitussive, expectorant, decongestant, antihistamine drugs, local anesthetics, and the like.

[0208] The invention disclosed herein is meant to encompass the use of any pharmaceutically acceptable salts thereof of the disclosed opioid analgesics. The pharmaceutically acceptable salts include, but are not limited to, metal salts such as sodium salt, potassium salt, sodium salt and the like; alkaline earth metals such as calcium salt, magnesium salt and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and the like; inorganic acid salts such as hydrochloride, hydrobromide, sulfate, phosphate and the like; organic acid salts such as formate, acetate, trifluoroacetate, maleate, tartrate and the like; sulfonates such as methane-sulfonate, benzenesulfonate, p-toluenesulfonate, and the like; amino acid salts such as arginate, asparagine, glutamate and the like.

[0209] Some of the opioid analgesics disclosed herein may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass the use of any of such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified

otherwise, it is intended to include both E and Z geometric isomers. The use of all tautomers are intended to be encompassed by the present invention as well.

[0210] The oral dosage forms of the present invention may be in the form of tablets, troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, etc.

[0211] In certain embodiments, the present invention provides for a method of preventing abuse of an oral controlled release dosage form of an opioid analgesic comprising preparing the dosage forms as described above.

[0212] In certain embodiments, the present invention provides for a method of preventing diversion of an oral controlled release dosage form of an opioid analgesic comprising preparing the dosage forms as described above.

[0213] In certain embodiments, the present invention provides for a method of treating pain by administering to a human patient the dosage forms described above.

[0214] The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

#### EXAMPLE 1

A 20 mg Oxycodone Formulation is Prepared  
Containing Naloxone as the Antagonist and  
Xanthan Gum as the Aversive Agent

[0215] In this example, a small amount of xanthan gum is added to the oxycodone formulation during the granulation process. Other gelling agents such as curdlan, carrageenan, alginates, pectin, gelatin, furcelleran, agar, guar gum, locust bean gum, tara gum, tragacanth, acacia, glucomannans, karaya, starch and starch derivatives, egg white powder, lacto albumin, soy protein, Jargel, gellan gum, welan gum, rhamosan gum, and the like, could also be used as gelling agents. Other semi-synthetic materials such as chitosan, pullulan, polyallevulan, hydroxypropyl cellulose, methylcellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, ethylhydroxyethyl cellulose, all ether derivatives of cellulose, and the like, could also be used as alternate gelling materials. The formulation of Example 1 is listed in Table 1 below.

TABLE 1

| Ingredients             | Amt/Unit (mg) | Amount/Batch (gm) |
|-------------------------|---------------|-------------------|
| Oxycodone HCl           | 20.0          | 209.6*            |
| Spray Dried Lactose     | 59.25         | 592.5             |
| Povidone                | 5.0           | 50.0              |
| Eudragit RS30D (solids) | 10.0          | 100               |
| Triacetin               | 2.0           | 20.0              |
| Naloxone HCl            | 0.61          | 6.12**            |
| Xanthan gum             | 9.0           | 90.0              |
| Stearyl Alcohol         | 25.0          | 250.0             |
| Talc                    | 2.5           | 25.0              |
| Magnesium Stearate      | 1.25          | 12.5              |
| Opadry Pink Y-S-14518A  | 5.0           | 50.0              |

\*adjusted for 99.6% assay and 4.2% residual moisture.

\*\*adjusted for 99.23% assay and 0.5% residual moisture.

#### [0216] Process

[0217] 1. Dispersion: Dissolve naloxone HCl in water and the solution is added to the Eudragit/Triacetin dispersion.

[0218] 2. Granulation: Spray the Eudragit/Triacetin dispersion onto the oxycodone HCl, Spray Dried Lactose, xanthan gum and Povidone using a fluid bed granulator.

[0219] 3. Milling: Discharge the granulation and pass through a mill

[0220] 4. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.

[0221] 5. Milling: Pass the cooled granulation through a mill.

[0222] 6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.

[0223] 7. Compression: Compress the granulation into tablets using a tablet press.

#### EXAMPLE 2

A 40 mg Oxycodone Formulation was Prepared Containing Naloxone as the Antagonist and Xanthan Gum as the Aversive Agent

[0224] To determine the effect of varying amount of xanthan gum on the gelling property and dissolution rate of an oxycodone tablet, three levels of xanthan gum were added to 40 mg oxycodone granulation and compressed into tablets. Oxycodone recovery from water extraction of the tablet and the drug release rate were determined. The oxycodone granulation formulation of Example 2 is listed in Table 2 below.

TABLE 2

| Ingredients             | Amt/Unit (mg) |
|-------------------------|---------------|
| Oxycodone HCl           | 40.0          |
| Spray Dried Lactose     | 39.25         |
| Povidone                | 5.0           |
| Eudragit RS30D (solids) | 10.0          |
| Triacetin               | 2.0           |
| Naloxone HCL            | 0.9           |
| Stearyl Alcohol         | 25.0          |
| Talc                    | 2.5           |
| Magnesium Stearate      | 1.25          |
| Total                   | 125.9         |

[0225] Examples 2A to 2C were prepared adding different amounts (3 mg, 5 mg, and 9 mg) of xanthan gum to a 125.9 mg oxycodone granulation of Example 2.

| Ingredients           | Amt/Unit (mg) |
|-----------------------|---------------|
| <u>EXAMPLE 2A</u>     |               |
| Oxycodone granulation | 125.9         |
| Xanthan gum           | 3             |
| Total                 | 128.9         |
| <u>EXAMPLE 2B</u>     |               |
| Oxycodone granulation | 125.9         |
| Xanthan gum           | 5             |
| Total                 | 130.9         |

-continued

| Ingredients           | Amt/Unit (mg) |
|-----------------------|---------------|
| <u>EXAMPLE 2C</u>     |               |
| Oxycodone granulation | 125.9         |
| Xanthan gum           | 9             |
| Total                 | 134.9         |

#### [0226] Process

[0227] 1. Dispersion: Dissolve naloxone HCl in water and the solution is added to the Eudragit/Triacetin dispersion.

[0228] 2. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.

[0229] 3. Milling: Discharge the granulation and pass through a mill.

[0230] 4. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.

[0231] 5. Milling: Pass the cooled granulation through a mill.

[0232] 6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.

[0233] 7. Add xanthan gum (3 levels) to the granulation and mix well.

[0234] 8. Compression: Compress the granulation into tablets using a tablet press.

#### EXAMPLE 3

[0235] The granulation of Example 2 was compressed into tablets using a tablet press without the addition of xanthan gum, and Examples 2, 2A-C were tested under the following dissolution conditions and gave the results listed in Table 3 below.

[0236] 1. Apparatus: USP Type II (paddle), 150 rpm.

[0237] 2. Medium: 700 ml SGF for first hour, thereafter made 900 ml with phosphate buffer to pH 7.5.

[0238] 3. Sampling time: 1,2,4,8,12,18 and 24 hours.

[0239] 4. Analytical: High Performance Liquid Chromatography.

TABLE 3

| <u>Dissolution Results</u> |                             |                             |                             |                                   |       |
|----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------------|-------|
| <u>% Dissolved</u>         |                             |                             |                             |                                   |       |
| Time (hrs)                 | Ex. 2A<br>(3 mg<br>xanthan) | Ex. 2B<br>(5 mg<br>xanthan) | Ex. 2C<br>(9 mg<br>xanthan) | Ex. 2<br>(no<br>xanthan<br>added) | Spec  |
| 1                          | 48                          | 43                          | 46                          | 45                                | 28-58 |
| 4                          | 86                          | 73                          | 79                          | 75                                | 55-88 |
| 12                         | 101                         | 98                          | 99                          | 93                                | >80   |

[0240] The dissolution results show that all the tablets prepared have similar dissolution profiles. The inclusion of xanthan gum does not appear to substantially change the oxycodone dissolution rate.

[0241] When 1 mL of water was added to the tablets containing xanthan gum on a tea spoon, the solution was not viscous. However, when the samples were heated and allowed to cool, the samples became very viscous. It was very difficult to withdraw this gel-like solution into a syringe for injection.

#### EXAMPLE 4

A 20 mg Oxycodone Formulation Containing Naloxone as the Antagonist and a Bittering Agent as the Aversive Agent is Prepared

[0242] In this example, a small amount of denatonium benzoate is added to an oxycodone formulation during the granulation process. The bitter taste would reduce the abuse of oxycodone by oral or intranasal route. The oxycodone formulation of Example 4 is listed in Table 4 below.

TABLE 4

| Ingredients             | Amt/Unit (mg) | Amount/Batch (gm) |
|-------------------------|---------------|-------------------|
| Oxycodone HCl           | 20.0          | 209.6*            |
| Spray Dried Lactose     | 59.25         | 592.5             |
| Povidone                | 5.0           | 50.0              |
| Eudragit RS30D (solids) | 10.0          | 100               |
| Triacetin               | 2.0           | 20.0              |
| Naloxone HCl            | 0.61          | 6.12**            |
| Denatonium benzoate     | 0.07          | 0.68              |
| Stearyl Alcohol         | 25.0          | 250.0             |
| Talc                    | 2.5           | 25.0              |
| Magnesium Stearate      | 1.25          | 12.5              |
| Opadry Pink Y-S-14518A  | 5.0           | 50.0              |

\*adjusted for 99.6% assay and 4.2% residual moisture.

\*\*adjusted for 99.23% assay and 0.5% residual moisture.

#### [0243] Process

[0244] 1. Dispersion: Dissolve naloxone HCl and denatonium benzoate in water and the solution is added to the Eudragit/Triacetin dispersion.

[0245] 2. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.

[0246] 3. Milling: Discharge the granulation and pass through a mill.

[0247] 4. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.

[0248] 5. Milling: Pass the cooled granulation through a mill.

[0249] 6. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.

[0250] 7. Compression: Compress the granulation into tablets using a tablet press.

#### EXAMPLE 5

[0251] In Example 5, a substantially non-releasable form of a bittering agent (denatonium benzoate) is prepared by coating denatonium benzoate particles with a coating that

renders the denatonium benzoate substantially non-releasable. The formulation of Example 5 is listed in Table 5 below.

TABLE 5

| Ingredients                                                                             | Amt/unit (mg) |
|-----------------------------------------------------------------------------------------|---------------|
| <b>LOADING</b>                                                                          |               |
| denatonium benzoate                                                                     | 0.07          |
| Sugar Spheres (30/35 mesh)                                                              | 50.0          |
| Opadry White Y-5-7068                                                                   | 2.5           |
| Purified Water                                                                          | 42.5*         |
| <b>OVERCOATING</b>                                                                      |               |
| Opadry White Y-5-7068                                                                   | 3.02          |
| Purified Water                                                                          | 17.11*        |
| <b>NON-RELEASE COATING (FOR RENDERING BITTERING AGENT SUBSTANTIALLY NON-RELEASABLE)</b> |               |
| Eudragit RS30D (dry wt.)                                                                | 12.10         |
| Triethyl Citrate                                                                        | 2.42          |
| Talc                                                                                    | 4.84          |
| Purified Water                                                                          | 49.21*        |
| <b>OVERCOATING</b>                                                                      |               |
| Opadry White Y-5-7068                                                                   | 4.12          |
| Purified Water                                                                          | 23.35*        |
| Total                                                                                   | 79.07         |

\*Remains in product as residual moisture only.

#### [0252] Process:

[0253] 1. Solution Preparation Dissolve the denatonium benzoate in Purified Water. Once dissolved, add the Opadry White and continue mixing until a homogeneous dispersion is yielded.

[0254] 2. Loading Apply the above dispersion onto the Sugar Spheres using a fluid bed coating machine.

[0255] 3. Overcoating Prepare an overcoating solution by dispersing Opadry White in Purified Water. Apply this dispersion over the sugar spheres loaded with denatonium benzoate using a fluid bed coating machine.

[0256] 4. Retardant Coating Prepare the non-release coating solution by mixing the Eudragit RS30D, Triethyl Citrate, Talc, and Purified Water. Apply this dispersion over the loaded and overcoated sugar spheres using a fluid bed coating machine.

[0257] 5. Overcoating Prepare a second overcoating solution by dispersing Opadry White in Purified Water. Apply this dispersion over the non-release coated denatonium benzoate spheres using a fluid bed coating machine.

[0258] 6. Curing Cure the spheres at 45° C. for approximately 48 hours.

#### EXAMPLE 6

[0259] In Example 6, a substantially non-releasable form of a bittering agent (denatonium benzoate) is prepared as denatonium benzoate containing granulates. The granulates



are comprised of denatonium benzoate dispersed in a matrix that renders the denatonium benzoate substantially non-releasable. The formulation of Example 6 is listed in Table 6 below.

TABLE 6

| Ingredient                                                     | Amt/unit (mg) |
|----------------------------------------------------------------|---------------|
| Denatonium benzoate                                            | 0.07          |
| Dicalcium Phosphate                                            | 53.0          |
| Poly (DI-Lactide-Co-Glycolide) polymner (PLGA)<br>MW ~ 100,000 | 12.0          |
| Ethyl Acetate                                                  |               |
| Total                                                          | 65.07         |

\*Used as a vehicle for application of PLGA polymer.

**[0260] Process:**

**[0261]** 1. Solution Preparation Dissolve PLGA in Ethyl Acetate by mixing.

**[0262]** 2. Granulation Place the denatonium benzoate, and Dicalcium Phosphate in a fluid bed coating machine and granulate by spraying the above solution. 200.1146US

**EXAMPLE 7**

**[0263]** In Example 7, a substantially non-releasable form of a bittering agent (denatonium benzoate) is prepared as denatonium benzoate extruded pellets. The formulation of Example 7 is listed in Table 7 below.

TABLE 7

| Ingredient         | Amt/unit (mg) |
|--------------------|---------------|
| Dantonium benzoate | 0.07          |
| Eudragit RSPO      | 180.0         |
| Stearyl Alcohol    | 55.0          |
| Total              | 235.07        |

**[0264] Process:**

**[0265]** 1. Milling Pass stearyl alcohol flakes through an impact mill.

**[0266]** 2. Blending Mix Denatonium benzoate, Eudragit, and milled Stearyl Alcohol in a twin shell blender.

**[0267]** 3. Extrusion Continuously feed the blended material into a twin screw extruder and collect the resultant strands on a conveyor.

**[0268]** 4. Cooling Allow the strands to cool on the conveyor.

**[0269]** 5. Pelletizing Cut the cooled strands into pellets using a Pelletizer.

**[0270]** 6. Screening Screen the pellets and collect desired sieve portion.

**EXAMPLE 8**

**Naltrexone HCl Beads**

**[0271]** In Example 8, Naltrexone HCl beads for incorporation into capsules were prepared having the following formulation in Table 8 below.

TABLE 8

|                                | Ingredients                     | Amt/unit (mg) |
|--------------------------------|---------------------------------|---------------|
| Step 1. Drug layering          | Naltrexone HCl                  | 2.1           |
|                                | Non-pareil beads (30/35 mesh)   | 39.98         |
|                                | Opadry Clear                    | 0.4           |
|                                | (Hydroxypropylmethyl cellulose  |               |
| Step 2. Anionic polymer coat   | Sodium ascorbate                | 0.027         |
|                                | Ascorbic acid                   | 0.05          |
|                                | Eudragit L30D (dry)             | 2.164         |
|                                | Triethyl Citrate                | 0.433         |
| Step 3. Sustained release coat | Cabosil                         | 0.108         |
|                                | Eudragit RS30D (dry)            | 17.475        |
|                                | Triethyl citrate                | 3.495         |
|                                | Cabosil                         | 0.874         |
| Step 4. Seal coat              | Opadry Clear                    | 1.899         |
|                                | (Hydroxypropylmethyl cellulose) |               |
|                                | Cabosil                         | 0.271         |
| Total (on dry basis)           |                                 | 69.287        |

**[0272] Process:**

**[0273]** 1. Dissolve naltrexone HCl, ascorbic acid, sodium ascorbate and Opadry Clear in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.

**[0274]** 2. Disperse Eudragit L30D, Triethyl citrate, and Cabosil in water. Spray the dispersion onto the drug-loaded beads in the fluid bed coater.

**[0275]** 3. Disperse Eudragit RS30D, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.

**[0276]** 4. Dissolve Opadry Clear in water. Spray the solution onto the beads in the fluid bed coater.

**[0277]** 5. Cure the beads at 60° C. for 24 hours.

**EXAMPLE 9**

**Naltrexone Multiparticulates**

**[0278]** A naltrexone melt extruded multiparticulate formulation was prepared. The melt extruded multiparticulate formulation is listed in Table 9 below.

TABLE 9

| Ingredients     | Amt/Unit (mg) |
|-----------------|---------------|
| Naltrexone HCl  | 2.0           |
| Eudragit RSPO   | 88.0          |
| Stearyl alcohol | 15.0          |
| Stearic acid    | 15.0          |
| BHT             | 1.0           |
| Total           | 121.0         |



**[0279]** Process:

**[0280]** 1. Blend milled Stearic acid, stearyl alcohol, Naltrexone HCl, BHT, and Eudragit RSPO using a V-blender.

**[0281]** 2. Extrude the mixture using a Powder Feeder, Melt Extruder(equipped with the 6×1 mm die head), Conveyor, Lasermike, and Pelletizer.

**[0282]** Powder feed rate—4.2 kg/hr; vacuum—~980 mBar

**[0283]** Conveyor—such that diameter of extrudate is 1 mm

**[0284]** Pelletizer—such that pellets are cut to 1 mm in length

**[0285]** 3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen.

**[0286]** 4. Fill size #2 clear gelatin capsules with the pellets. Range: NLT 114 mg and NMT 126 mg.

## EXAMPLE 10

## Naltrexone CR Beads

**[0287]** A naltrexone sustained release bead formulation was prepared which can be incorporated into an opioid controlled release granulation and compressed into tablets. The naltrexone controlled release bead formulation is listed in Table 10 below.

TABLE 10

|                                | Ingredients                     | Amt/unit*<br>(mg) |
|--------------------------------|---------------------------------|-------------------|
| Step 1. Drug layering          | Naltrexone HCl                  | 0.609             |
|                                | Non-pareil beads (30/35 mesh)   | 67.264            |
|                                | Opadry Clear                    | 0.547             |
| Step 2. Seal coat              | Eudragit L                      | 2.545             |
|                                | Triethyl citrate                | 0.636             |
|                                | Glyceryl monostearate           | 0.239             |
| Step 3. Sustained release coat | Eudragit RS30D (dry)            | 43.789            |
|                                | Triethyl citrate                | 8.758             |
|                                | Cabosil                         | 2.189             |
| Step 4. Seal coat              | Opadry Clear                    | 2.053             |
|                                | (Hydroxypropylmethyl cellulose) |                   |
|                                | Cabosil                         | 1.368             |
| Total                          |                                 | 130               |

**[0288]** Process:

**[0289]** 1. Dissolve naltrexone HCl and Opadry (HPMC) in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.

**[0290]** 2. Disperse Eudragit L, Triethyl citrate, and glyceryl monostearate in water. Spray the dispersion onto the drug-loaded beads in the fluid bed coater.

**[0291]** 3. Disperse Eudragit RS, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.

**[0292]** 4. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater.

**[0293]** 5. Cure the beads at 60° C. for 24 hours.

## EXAMPLE 11

## Controlled-Release Oxycodone

**[0294]** In Example 11, a sustained release 20 mg controlled release oxycodone formulation was prepared having the formulation listed in Table 11 below.

TABLE 11

| Ingredients             | Amt/Unit (mg) |
|-------------------------|---------------|
| Oxycodone HCl           | 20.0          |
| Spray Dried Lactose     | 59.25         |
| Povidone                | 5.0           |
| Eudragit RS30D (solids) | 10.0          |
| Triacetin               | 2.0           |
| Stearyl Alcohol         | 25.0          |
| Talc                    | 2.5           |
| Magnesium Stearate      | 1.25          |
| Opadry Pink Y-S-14518A  | 4.0           |
| Total                   | 129.0         |

**[0295]** Process:

**[0296]** 1. Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose and Povidone using a fluid bed granulator.

**[0297]** 2. Milling: Discharge the granulation and pass through a mill.

**[0298]** 3. Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.

**[0299]** 4. Milling: Pass the cooled granulation through a mill.

**[0300]** 5. Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.

**[0301]** 6. Compression: Compress the granulation into tablets using a tablet press.

**[0302]** 7. Film coating: Apply an aqueous film coat to the tablets.

## EXAMPLE 12

**[0303]** In Example 12, naltrexone beads prepared in accordance with Example 16 are incorporated into the sustained release 20 mg oxycodone tablets prepared in accordance with Example 11 and having the formula listed in Table 12 below.

TABLE 12

|                     | Ingredients          | Amt/unit*<br>(mg) |
|---------------------|----------------------|-------------------|
| Step 1. Granulation | Oxycodone HCl        | 20.0              |
|                     | Spray Dried Lactose  | 59.25             |
|                     | Povidone             | 5.0               |
|                     | Eudragit RS30D (dry) | 10.0              |
|                     | Triacetin            | 2.0               |

TABLE 12-continued

|                            | Ingredients                       | Amt/unit*<br>(mg) |
|----------------------------|-----------------------------------|-------------------|
| Step 2. Combination tablet | Stearyl alcohol                   | 25.0              |
|                            | Talc                              | 2.5               |
|                            | Magnesium                         | 1.25              |
|                            | OxyContin granulation (Example 3) | 125               |
|                            | Naltrexone CR beads (Formula 2)   | 140               |

**[0304] Process:**

**[0305]** 1. Spray the Eudragit/triacetin dispersion onto the Oxycodone HCl, spray dried lactose and povidone using a fluid bed granulator.

**[0306]** 2. Discharge the granulation and pass through a mill.

**[0307]** 3. Melt the stearyl alcohol and add to the milled granulation using a mill. Allow to cool.

**[0308]** 4. Pass the cooled granulation through a mill.

**[0309]** 5. Lubricate the granulation with talc and magnesium stearate. Using a mixer.

**[0310]** 6. Mix naltrexone beads with the above granulation and compress into tablets.

**[0311] Alternate Process:**

**[0312]** 1. Spray the Eudragit/triacetin dispersion onto the Oxycodone HCl, spray dried lactose and povidone using a fluid bed granulator.

**[0313]** 2. Discharge the granulation and pass through a mill.

**[0314]** 3. Mix naltrexone beads (example 2) with the above granulation in a Hobart mixer.

**[0315]** 4. Melt the stearyl alcohol and add to the above mixture. Allow to cool.

**[0316]** 5. Pass the cooled granulation through a mill.

**[0317]** 6. Lubricate the granulation with talc and magnesium stearate using a mixer.

**[0318]** 7. Compress into tablets.

**[0319]** Releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in an Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

**[0320]** One or more aversive agents as described herein can be incorporated into the oxycodone tablets by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof.

**EXAMPLE 13****Controlled Release Hydrocodone**

**[0321]** A sustained release hydrocodone formulation was prepared having the formula in Table 13 below.

TABLE 13

| Ingredients            | Amt/Unit (mg) | Amt/Batch (g) |
|------------------------|---------------|---------------|
| Hydrocodone Bitartrate | 15.0          | 320.0         |
| Eudragit RSPO          | 76.0          | 1520.0        |
| Eudragit RLPO          | 4.0           | 80.0          |
| Stearyl Alcohol        | 25.0          | 500.0         |
| Total                  | 120.0         | 2400.0        |

**[0322] Process:**

**[0323]** 1. Blend milled Stearyl Alcohol, Eudragit RLPO, Hydrocodone Bitartrate, and Eudragit RSPO using a Hobart Mixer.

**[0324]** 2. Extrude the granulation using a Powder Feeder, Melt Extruder (equipped with the 6x1 mm die head), Conveyor, Lasermike, and Pelletizer.

**[0325]** Powder feed rate—40 g/min; vacuum—~980 mBar

**[0326]** Conveyor—such that diameter of extrudate is 1 mm

**[0327]** Pelletizer—such that pellets are cut to 1 mm in length

**[0328]** 3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen.

**[0329]** 4. Fill size #2 clear gelatin capsules with the pellets. Range: NLT (not less than) 114 mg and NMT (not more than) 126 mg.

**[0330]** The sequestered naltrexone formulation of Example 9 can be incorporated in a capsule with the hydrocodone pellets. Preferably, the sequestered naltrexone pellets are indistinguishable from the hydrocodone pellets.

**[0331]** Releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in an Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

**[0332]** One or more aversive agents as described herein can be incorporated into a capsule with the hydrocodone pellets, into the hydrocodone pellets, or on the hydrocodone pellets by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof. Preferably, when pellets comprising the aversive agent(s) are incorporated into the capsule they are indistinguishable from the hydrocodone pellets.

## EXAMPLE 14

## Oxycodone HCl Beads

[0333] A sustained release oxycodone HCl bead formulation was prepared having the formula in Table 14 below.

TABLE 14

|                                | Ingredients                     | Amt/unit*<br>(mg) |
|--------------------------------|---------------------------------|-------------------|
| Step 1. Drug layering          | Oxycodone HCl                   | 10.5              |
|                                | Non-pareil beads (30/35 mesh)   | 45,349            |
|                                | Opadry Clear                    | 2.5               |
|                                |                                 |                   |
| Step 2. Sustained release coat | Eudragit RS30D (dry)            | 7.206             |
|                                | Eudragit RL30D (dry)            | 0.379             |
|                                | Triethyl citrate                | 1.517             |
|                                | Cabosil                         | 0.379             |
| Step 3. Seal coat              | Opadry Clear                    | 1.899             |
|                                | (Hydroxypropylmethyl cellulose) |                   |
|                                | Cabosil                         | 0.271             |
|                                |                                 |                   |
| Total                          |                                 | 70.0              |

[0334] Process:

[0335] 1. Dissolve oxycodone HCl and Opadry (HPMC) in water. Spray the drug solution onto non-pareil beads in a fluid bed coater with Wurster insert.

[0336] 2. Disperse Eudragit RS, Eudragit RL, triethyl citrate, and Cabosil in water. Spray the dispersion onto the beads in the fluid bed coater.

[0337] 3. Dissolve Opadry in water. Spray the solution onto the beads in the fluid bed coater.

[0338] 4. Cure the beads at 60° C. for 24 hours.

[0339] The sequestered naltrexone formulation of Example 8 can be incorporated in a capsule with the oxycodone beads. Preferably, the sequestered naltrexone beads are indistinguishable from the oxycodone beads.

[0340] Releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in an Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

[0341] One or more aversive agents as described herein can be incorporated into a capsule with the oxycodone beads, into the oxycodone beads, or on the oxycodone beads by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof. Preferably, when beads comprising the aversive agent(s) are incorporated into the capsule they are indistinguishable from the oxycodone beads.

## EXAMPLE 15

Controlled Release Hydromorphone A sustained release hydromorphone HCl formulation was prepared having the formula in Table 15 below:

[0342]

TABLE 15

| Ingredients       | Amt/Unit (mg) |
|-------------------|---------------|
| Hydromorphone HCl | 12.0          |
| Eudragit RSPO     | 76.5          |
| Ethocel           | 4.5           |
| Stearic acid      | 27.0          |
| Total             | 120.0         |

[0343] Process:

[0344] 1. Blend milled Stearic acid, ethocel, Hydrocodone Bitartrate, and Eudragit RSPO using a V-blender.

[0345] 2. Extrude the mixture using a Powder Feeder, Melt Extruder (equipped with the 6×1 mm die head), Conveyor, Lasermike, and Pelletizer.

[0346] Powder feed rate—4.2 kg/hr; vacuum—~980 mBar

[0347] Conveyor—such that diameter of extrudate is 1 mm

[0348] Pelletizer—such that pellets are cut to 1 mm in length

[0349] 3. Screen pellets using #16 mesh and #20 mesh screens. Collect material that passes through the #16 mesh screen and is retained on the #20 mesh screen.

[0350] 4. Fill size #2 clear gelatin capsules with the pellets. Range: NLT 114 mg and NMT 126 mg.

[0351] The sequestered naltrexone formulation of Example 15 can be incorporated in a capsule with the hydromorphone pellets. Preferably, the sequestered naltrexone pellets are indistinguishable from the hydromorphone pellets.

[0352] Releasable naltrexone can be a) overcoated onto the pellets by e.g., including it in an Opadry solution, b) modifying the sequestered component to release the desired naltrexone, c) including the naltrexone with the opioid agonist; or included in any other method known in the art. The amount of naltrexone should be in an amount to have a desired pharmacological effect as disclosed herein and can be immediate or sustained release.

[0353] One or more aversive agents as described herein can be incorporated into a capsule with the hydromorphone pellets, into the hydromorphone pellets, or on the hydromorphone pellets by one skilled in the art. The one or more aversive agents may be in releasable, non-releasable, or substantially non-releasable form or a combination thereof. Preferably, when pellets comprising the aversive agent(s) are incorporated into the capsule they are indistinguishable from the hydromorphone pellets.

## EXAMPLE 16

A 20 mg Oxycodone Dosage Form Containing  
Naloxone as the Antagonist and Multiple Detering  
Agents is Prepared

[0354] Various deterring agents used in the previous examples are combined in one product to produce a tablet which could provide tampering resistance to multiple types of abuse by the addicts. A small amount of naloxone hydrochloride, denatonium benzoate, and xanthan gum are added to an oxycodone formulation during the granulation process. The oxycodone granulation formulation of Example 16 is listed in Table 16 below.

TABLE 16

| Ingredients             | Amt/Unit (mg) | Amount/Batch (gm) |
|-------------------------|---------------|-------------------|
| Oxycodone HCl           | 20.0          | 209.6*            |
| Spray Dried Lactose     | 59.25         | 592.5             |
| Povidone                | 5.0           | 50.0              |
| Eudragit RS30D (solids) | 10.0          | 100               |
| Triacetin               | 2.0           | 20.0              |
| Naloxone HCl            | 0.61          | 6.12**            |
| Denatonium benzoate     | 0.07          | 0.68              |
| Xanthan gum             | 9.0           | 90.0              |
| Stearyl Alcohol         | 25.0          | 250.0             |
| Talc                    | 2.5           | 25.0              |
| Magnesium Stearate      | 1.25          | 12.5              |
| Opadry Pink Y-S-14518A  | 5.0           | 50.0              |

\*adjusted for 99.6% assay and 4.2% residual moisture.

\*\*adjusted for 99.23% assay and 0.5% residual moisture.

## [0355] Process

[0356] Dispersion: Dissolve naloxone HCL and denatonium benzoate in water and the solution is added to the Eudragit/Tracetin dispersion.

[0357] Granulation: Spray the Eudragit/Triacetin dispersion onto the Oxycodone HCl, Spray Dried Lactose, xanthan gum and Povidone using a fluid bed granulator.

[0358] Milling: Discharge the granulation and pass through a mill.

[0359] Waxing: Melt the stearyl alcohol and add to the milled granulation using a mixer. Allow to cool.

[0360] Milling: Pass the cooled granulation through a mill.

[0361] Lubrication: Lubricate the granulation with talc and magnesium stearate using a mixer.

[0362] Compression: Compress the granulation into tablets using a tablet press.

## EXAMPLE 17-20

[0363] Examples 4-7 can be repeated utilizing a sufficient amount of capsaicin in place of, or in addition to the aversive agents disclosed therein.

[0364] While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that obvious modifications can be made herein without departing from the spirit and scope of the invention. Such variations are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A oral dosage form comprising:

a therapeutically effective amount of an opioid analgesic; an opioid antagonist; and

an irritant in an effective amount to impart an irritating sensation to an abuser upon administration of said dosage form after tampering.

2. The oral dosage form of claim 1, wherein the irritant is selected from the group consisting of capsaicin, a capsaicin analog, and mixtures thereof.

3. The oral dosage form of claim 1, wherein the irritant is a capsaicin analog selected from the group consisting of resiniferatoxin, tinyatoxin, heptanoylisobutylamide, heptanoyl guaiacylamide, other isobutylamides or guaiacylamides, dihydrocapsaicin, homovanillyl octylester, nonanoyl vanillylamide, and mixtures thereof.

4. The oral dosage form of claim 1, wherein the irritant is capsaicin.

5. The oral dosage form of claim 1, wherein the irritant is vanillylamide.

6. The oral dosage form of claim 1, wherein the irritant is in a sequestered form.

7. The oral dosage form of claim 1, wherein the antagonist is in a sequestered form.

8. The oral dosage form of claim 1, wherein the antagonist and the irritant are both in sequestered forms.

9. The oral dosage form of claim 1, wherein the irritant is in an amount of about 0.00125% to about 50% by weight of the dosage form.

10. The oral dosage form of claim 1, wherein the irritant is in an amount of about 1 to about 7.5% by weight of the dosage form.

11. The oral dosage form of claim 1, wherein the irritant is in an amount of about 1 to about 5% by weight of the dosage form.

12. The oral dosage forms of claim 1, further comprising a pharmaceutically acceptable excipient

13. The oral dosage forms of claim 12, wherein said excipient is a sustained release excipient.

14. The oral dosage form of claim 12, said dosage form providing an analgesic effect for at least about 12 hours after oral administration to a human patient.

15. The oral dosage form of claim 1, wherein said irritant is at least partially interdispersed with the opioid analgesic.

16. The dosage form of claim 1, having a ratio of opioid antagonist to opioid agonist that is analgesically effective when the combination is administered orally, but which is aversive in physically dependent human subjects when administered at the same amount or at a higher amount than said therapeutically effective amount.

17. The dosage form of claim 16, wherein said ratio of opioid antagonist to opioid agonist maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist relative to the same therapeutic amount of opioid analgesic when administered to human patients without said opioid antagonist.

18. The oral dosage form of claim 1 wherein the antagonist is in an amount to attenuate a side effect of said opioid agonist selected from the group consisting of anti-analgesia, hyperalgesia, hyperexcitability, physical dependence, tolerance, and a combination of any of the foregoing.

**19.** The oral dosage form of claim 1, wherein the amount of antagonist released during the dosing interval enhances the analgesic potency of the opioid agonist.

**20.** The oral dosage form of claim 1, wherein the amount of the releasable opioid receptor antagonist is about 100 to about 1000 fold less than the amount of the opioid agonist.

**21.** A method of treating pain comprising administering to a patient an oral dosage form of claim 1.

**22.** A method of preparing a pharmaceutical dosage form comprising combining a therapeutically effective amount of an opioid analgesic; and an antagonist in a dosage form with an effective amount of a irritant to impart an irritating sensation to an abuser upon administration of said dosage form after tampering.

**23.** The method of claim 22, wherein said irritant is at least partially interdispersed with the opioid analgesic.

**24.** A method of preventing abuse of an oral dosage form of an opioid analgesic comprising:

preparing the dosage form with an analgesically effective amount of an opioid analgesic; an opioid antagonist; and

an irritant in an effective amount to impart an irritating sensation to an abuser upon administration of said dosage form after tampering.

\* \* \* \* \*